PB 178129

ENVIRONMENTAL HEALTH SERIES

Radiological Health

REDUCTION OF RADIATION EXPOSURE IN NUCLEAR MEDICINE

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

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REDUCTION OF RADIATION EXPOSURE IN NUCLEAR MEDICINE

Proceedings of a Symposium
held at the
Kellogg Center for Continuing Education
Michigan State University
East Lansing, Mich.

August 7-9, 1967

Edited by

Kenneth D. Williams
James F. Cooper
Raymond T. Moore, M.D.
Albert W. Hilberg, M.D.

Cosponsored by the National Center for Radiological Health and the Michigan State University College of Human Medicine, Institute of Biology and Medicine, and the Continuing Education Service under Contract No. PH 86-68-16.

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
Bureau of Disease Prevention and Environmental Control
National Center for Radiological Health
Rockville, Maryland 20852

Library of Congress catalog card number 68-60014

Public Health Service Publication No. 999-RH-30
December 1967

U.S. GOVERNMENT PRINTING OFFICE, WASHINGTON : 1967

FOREWORD

Within the U.S. Public Health Service, the National Center for Radiological Health (NCRH) has the primary responsibility for radiation protection activities. The primary activities may be described as: (1) investigation, surveillance and studies of radioactive contamination and other radiation hazards in the environment, (2) research and development in radiobiological effects and radiation exposure reduction and control methods, (3) training of specialists in the radiological health field, (4) technical assistance to State and local governments and other organizations, and (5) dissemination of information.

It is in accordance with the overall mission of the National Center for Radiological Health that this symposium was convened to more clearly define the areas in nuclear medicine which provide opportunities for increasing diagnostic information and reducing unproductive radiation exposure.

James G. Terrill, Jr.
Center Director
National Center for Radiological Health

PREFACE

This publication contains the proceedings of a symposium on the Reduction of Radiation Exposure in Nuclear Medicine, held on the campus of Michigan State University, East Lansing, Mich., August 7-9, 1967. The National Center for Radiological Health (NCRH) contracted with the Kellogg Center for Continuing Education to use their facilities and services for the symposium. The College of Human Medicine, the Institute of Biology and Medicine, and the Continuing Education Service of Michigan State University were cosponsors with the NCRH.

The program was designed to promote a free exchange of opinion; a full day was assigned to work group activity. However, the symposium was designed with an underlying theme throughout--obtaining the maximum reduction of radiation exposure from diagnostic nuclear medical procedures compatible with optimum medical benefit. The planning committee identified several sources of potential difficulties in nuclear medicine. First of all, the rapid growth of the field has resulted in an acute shortage of physicians and paramedical personnel trained in this specialty. Failure to achieve rapid and adequate dissemination of findings from research and development activities is another problem. Further, there is a definite need to standardize radiopharmaceutical formulation procedures within the hospital.

The main objectives of this forum were (1) to define more clearly the roles of the Atomic Energy Commission and the Public Health Service in nuclear medicine, (2) to review progress being made in certain problem areas, and (3) to conclude means for further reducing radiation exposure from diagnostic procedures while maintaining or increasing the information gained.

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ABSTRACT

Representatives from the nuclear medical community, industry, and governmental agencies attended a 3-day symposium, August 7-9, 1967, cosponsored by the National Center for Radiological Health and Michigan State University. Formal presentations, discussion sessions, and work-group reports are included in the proceedings.

Representatives of the Atomic Energy Commission and the National Center for Radiological Health defined the roles of these agencies in nuclear medicine. Professionals in the field of nuclear medicine presented the progress to date in the problem areas of internal radiation dosimetry, short half-lived radionuclides, instrumentation, radiopharmaceutical quality control, and manpower development. The work-group reports contain the conclusions resulting from a full day of work-group activity. The participants evaluated the need for reducing radiation exposure from nuclear medical procedures, formulated means that might be employed to use most efficiently the administered amount of radiopharmaceutical, and concluded possible solutions to problem areas in nuclear medicine.

ACKNOWLEDGMENTS

This symposium was arranged by the National Center for Radiological Health, Public Health Service, because of the interest expressed by members of various federal agencies and private organizations. Gratitude is expressed to all those who made this symposium possible and in particular to:

James G. Terrill, Jr., Center Director, National Center for Radiological Health, for his support and encouragement in this undertaking;

Eugene L. Saenger, M.D., Director, Radioisotope Laboratory, Cincinnati General Hospital; Henry N. Wellman, M.D., (Population Studies Program, NCRH) Chief, Nuclear Medicine Section, Cincinnati General Hospital; and Merrill A. Bender, M.D., Chief, Department of Nuclear Medicine, Roswell Park Memorial Institute, for their guidance in program planning;

Bruce W. Alderman, Conference Consultant, Kellogg Center for Continuing Education, Michigan State University, and his staff for arranging the necessary services and facilities for the symposium.

The editors are especially grateful to Mrs. Estelle Eisenberg, NCRH, for her tireless clerical assistance and to Mrs. Katharine Lyday, MSU, for undertaking the arduous task of technical editing.

Recognition is also due to the clerical and professional staff of the Medical and Occupational Radiation Program, NCRH, for their encouragement and assistance.

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PROGRAM

Monday, August 7, 1967

8:30 a.m.	Registration

FIRST GENERAL SESSION

Moderator - Albert W. Hilberg, M.D.

9:00 a.m.	Welcoming Remarks Andrew D. Hunt, Jr., M.D.
9:15 a.m.	Keynote Address Eugene L. Saenger, M.D.
10:00 a.m.	Role of AEC in Nuclear Medicine a. Function of the Division of Materials Licensing Richard E. Cunningham b. Function of the Medical Advisory Committee E. Richard King, M.D.
11:00 a.m.	Role of NCRH in Nuclear Medicine Raymond T. Moore, M.D.
11:30 a.m.	Panel Discussion
12:30 p.m.	GROUP LUNCHEON

SECOND GENERAL SESSION

Moderator - Herman L. Slatis, Ph.D.

2:00 p.m.	Internal Radiation Dosimetry Edward M. Smith, Sc.D.
2:20 p.m.	Discussion
2:30 p.m.	Production and Use of Short-Lived Isotopes Paul V. Harper, M.D.
2:50 p.m.	Discussion
3:00 p.m.	BREAK
3:20 p.m.	The Next Decade in Instrumentation Panel Discussion

Monday, August 7, 1967

3:50 p.m.	Radiopharmaceutical Quality Control Wilfred R. Konneker, Ph.D.
4:10 p.m.	Discussion
4:20 p.m.	Training and Manpower Development William H. Beierwaltes, M.D.
4:40 p.m.	Discussion
6:00 p.m.	GROUP DINNER Expectations of the Public Regarding Pharmaceuticals George F. Archambault

Tuesday, August 8, 1967

WORKSHOP

SESSION I

9:00 a.m.

The workshop, consisting of four work groups, will bring together the opinion of a diverse body of experience. Each work group will consider specific questions related to areas summarized in the second general session, and will be directed to conclude means for reducing radiation exposure from nuclear medicine procedures.

Work Group	Moderators
I	James L. Quinn, III, M.D. Henry Wellman, M.D.
II	William H. Briner Paul Numerof, Sc.D.
III	Thomas G. Mitchell, Ph.D. Donald W. Brown, M.D.
IV	E. Richard King, M.D. David Kuhl, M.D.

10:30 a.m.	BREAK
12:30 p.m.	GROUP LUNCHEON

Tuesday, August 8, 1967

WORKSHOP

SESSION II

2:00 p.m.	Continuation of Workshop
3:30 p.m.	BREAK
8:00 p.m.	Preparation of Reports by Work Group Moderators

Wednesday, August 9, 1967

THIRD GENERAL SESSION

Moderator - Albert W. Hilberg, M.D.

9:00 a.m. Reports by Work Group Moderators

Discussion of Reports

Summary
Merrill A. Bender, M.D.

Closing Remarks
Albert W. Hilberg, M.D.
Raymond T. Moore, M.D.

FIRST GENERAL SESSION

WELCOMING REMARKS

Andrew D. Hunt, Jr., M.D.[1]

I am always confused, Dr. Hilberg, as to what one says in a so-called welcoming speech when the real goal is to get this out of the way as soon as possible, and to get on with the real business. Some people talk about the shrubbery and the lovely trees we have on campus, and others talk about the weather (which maybe had better not be mentioned today). I will simply say a few words about the medical school since I have this opportunity at this moment and since we are very proud of what we are doing.

As you are aware Michigan State University is going through a rather fascinating transition from the status of being one of the country's first and leading agricultural colleges to becoming a very large and generalized multipurpose university. In the process of doing this, over the past 20 years an astonishingly complete set of typical basic sciences for medicine became established, serving such colleges as Veterinary Medicine and Natural Sciences. Also, a competent and varied selection of the behavioral and social sciences emerged on this campus so that when during the mid- and late-fifties there was much talk about the need for increasing the supply of physicians in the United States and when the concept of a 2-year medical school was given great impetus by the Kellogg Foundation and by the Association of American Colleges, it was decided that this university could in fact move into medicine with a fair amount of ease because of these large and well staffed basic science departments.

These departments, therefore, have been augmented and strengthened appropriately for the addition of medicine to their tasks. The behavioral and social sciences also have become involved; and over the last 3 years a strong basic science faculty has been accululated to develop the first phases of the medical school.

The really remarkable accomplishment, I think, has been that we now have a small class of 26 students that is concluding its first year working in existing facilities which have been moderately remodeled and revamped to accommodate them. One hundred and eithty acres have been set aside for further medical school development. We are now authorized by the State Board of

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[1] Dean of the College of Human Medicine, Michigan State University, East Lansing, Mich. 48823

Education to proceed to the full 4-year curriculum and we're actively planning and programming in this direction.

I think, if any of you would like to see what we have and hear in more detail some of our plans, we would be very happy to make such arrangements; and I have mentioned this to Dr. Hilberg who, I am sure, can work it out with you.

As I said before, welcome to our campus and thanks for your attention.

KEYNOTE ADDRESS

Eugene L. Saenger, M.D.[1]

This meeting has been convened to discuss the future directions of the field of nuclear medicine from the viewpoints of medical schools, practicing physicians, pharmaceutical suppliers, and representative branches of Government.

The purpose of this meeting might best be taken from the 1956 report of the NAS-NRC on "The Biological Effects of Atomic Radiation" (1) which states "The medical use of X rays should be reduced as much as is consistent with medical necessity." If the word "radionuclide" is substituted for "X rays" the purpose of this meeting is adequately defined.

Nuclear medicine may be defined in its broadest sense as encompassing all applications of radioactivity in the entire field of biology and medicine. In a somewhat more restrictive sense it is a specialty dealing with diagnostic and therapeutic applications of radionuclides. Its scope in addition to therapy is broad and diagnostically not as yet well explored. According to McAfee (2) there are eight categories of tracer methodology:

(1) Dynamics of the steady state.
(2) Transport across mucous membranes.
(3) Metabolic pathways and inter-conversions.
(4) Biological fate of chemically inert compounds including colloids.
(5) Mineral metabolism.
(6) Indicator dilution analysis.
(7) Regional blood flow.
(8) Spatial distribution.

It is in these groups that many further developments of clinical importance may be anticipated.

The reasons for holding such a conference at this time stem from the very rapid expansion and increasing complexity of nuclear medicine. At present it is a relatively small field not as yet well recognized by hospitals and medical schools although providing a truly unique approach to useful and safe (that is, nondestructive) tests for many diseases. It is this aspect which intrigues so many physicians outside of our specialty.

It is particularly encouraging to note that this symposium is being sponsored by the National Center for Radiological Health which in this way acts to provide a critical forum for the various representatives of different fields to debate these important problems in depth.

---

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Certainly all of us with clinical, investigative, and administrative responsibility recognize that a very careful and well-conceived course of action needs to be planned if maximum benefits are to be afforded to patients yet at the same time providing to them adequate protection and satisfactory quality control of the radioactive substances which we employ. Our task may be considered in several categories:

(1) Radiopharmaceuticals.
(2) Equipment and facilities.
(3) Manpower.
(4) Regulation.

RADIOPHARMACEUTICALS

The major clinical uses of nuclides have been achieved through the use of nuclides of 15 elements (I, Fe, Co, Cr, Hg, P, Na, K, Tc, Au, Sr, Se, Pd, H, C) for diagnostic purposes and nine for therapy (Ra, Sr, Rn, Co, Cs, Ir, Y, Cr, Ta) (3). The relatively small number of elements used diagnostically stems in part from the obvious fact that some of these elements constitute important body constituents. Yet at this time certain other important elements are not easily available (O, N, Mg).

There are a number of reasons for the limitation of these agents. First, the sources of production of crude isotopes, either reactors or cyclotrons, are geographically separated from the sites where the compounds are prepared and administered. Small cyclotrons designed for medical purposes have become available only lately. Even more recent is the development of higher energy linear accelerators which in addition to therapeutic uses are capable of producing particles for nuclide production and neutron activation analysis.

Most radiopharmaceuticals which are now available have been developed at medical centers rather than by pharmaceutical manufacturers. Thus it has been necessary for workers both to synthesize and test their own agents. This situation is somewhat unique to this field. Because of the special technical and protection problems of radiation, most commercial pharmaceutical programs have been started on very small scales and only in the past few years have the larger concerns entered this field. There have been many small companies with very limited capital who continue to make extremely important contributions to nuclear medicine. The larger companies supply the bulk of radionuclides for well-accepted clinical procedures. But the small companies have been the source of newer special compounds and have been very important in this regard particularly to the clinical investigator. In the further development of this field it will be essential to maintain an appropriate balance between these two types of suppliers.

Also as compared to many other aspects of nuclear energy such as reactor development and industrial applications, there has been very little Federal or other financial support for the commercial radiopharmaceutical companies.

The need to provide for the patient a safe, sterile, pyrogen free, chemically correct radioactive compound is one of the most difficult enigmas to be faced. The word "enigma" is used with purpose. To date I know of one documented case where patients received the wrong compounds (4) because of mislabeling. Two patients received 2.1 millicuries each of ^{32}P and two patients received less than 20 microcuries of ^{131}I labelled hippuran. One can always make the statement that there are many of these occurrences which are not reported and would be found were they intensively sought. Nevertheless the Atomic Energy Commission keeps very careful records of untoward events involving radiation incidents as provided for by law (5) and have failed to record additional episodes. Therefore one must conclude that at the patient level they do not exist.

There are of course a number of documented instances in which release of nuclides and contamination of personnel and laboratories have occurred in the preparation of radiopharmaceuticals but these events are of occupational concern only in the realm of health physics, do not require any new technological developments, and do not involve administration of drugs to patients.

The enigma revolves about certain facets of the radioactive properties of these materials. From the viewpoint of the doctor-patient relationship it is necessary to inject only compounds which would be as acceptable for insertion into the injector as into the injectee. There are well-accepted practices for the determination of sterility of stable pharmaceuticals. With many radioactive substances, however, the usual tests for sterility and pyrogenicity do not apply precisely since the actual compounds used have decayed prior to completion of the tests. Although it is possible to assay the precursors and the dregs, it is not possible to satisfy the well-accepted practices for such drug testing as they are now formulated. This question could generate some important new legal considerations. As yet no deleterious effects have been described from the current accepted practices as for example associated with ^{99m}Tc ion exchange columns or with the many pharmaceutical syntheses of labeled albumin and sulfides using this nuclide. Yet well-defined procedures for such testing are needed and it should be a purpose of this meeting to define appropriate methods.

A related problem is that of the storage and stability of labeled compounds. Bayly and Evans (6) have reviewed the radiolysis of biological compounds labeled with ^{3}H, ^{14}C, ^{35}S, ^{32}P, ^{125}I, ^{131}I, ^{57}Co and ^{58}Co and delineate the marked variability in stability of these substances. Compounds labeled with these nuclides are of limited use in clinical nuclear medicine at the moment. The reasons for this limited use arise from the fact that the physicians presently working in nuclear medicine have had little experience with the appropriate counting techniques and they are busy with scanning and other more acceptable methods. These compounds labeled with soft beta emitters are the most useful ones which can be found for studies of intermediary metabolism and their uses in clinical medicine can be expected to increase.

In an effort to obtain an estimate of the use of labeled compounds in investigative medicine, Volume 45 of the Journal of Clinical Investigation was reviewed for 1966 in order to provide an estimate of the use of new radioactive compounds.

There were 181 scientific papers. The articles were reviewed to determine whether the author used isotopic methods in human beings and whether the labeled compounds were those used routinely in clinical medicine (for example, ^{51}Cr blood volumes and ^{57}Co vitamin B-12 studies), or whether the papers utilized labeled compounds synthesized in the author's laboratory or by a pharmaceutical company as a "nonroutine" preparation. These "nonroutine" compounds administered to humans were utilized in 21 papers constituting 11 percent of the total papers. In most instances sterility was achieved by filtration through millipore filters. There were no reported reactions owing to pyrogens and no evidence of infection or other complications. Small numbers of human beings were involved--1 to 40 per study. Some were volunteers and some were patients chosen in a variety of ways.

It is reasonable to expect that the important advances in applying isotopic tests for practical clinical purposes will come from studies of the type described above. One of the important directives of medical research both from Congress and the Office of the President is that the results of such investigations be made available to the citizens of the United States as quickly as possible. Therefore a second purpose of this seminar could be the development of methodology to permit the continuation and expansion of these investigations. This problem will be discussed further under regulation.

EQUIPMENT AND FACILITIES

With the exception of the clinical programs of the AEC at Brookhaven, Oak Ridge, Chicago, Los Angeles, Berkeley, and a relatively small number of research and training grants at some medical centers there was relatively little support for development of equipment in nuclear medicine in the first two decades (1945-1965). This situation is not really different from that experienced in diagnostic radiology over a much longer period. Most of the important equipment advances in nuclear medicine have stemmed from equipment developed for other purposes. The one exception to this statement is the area of scanning and imaging where somewhat more adequate research and commercial funding has been provided in recent years.

Very little consideration has been given to providing such major facilities as medical cyclotrons and small reactors for production of short-lived isotopes and for activation analysis. A medical cyclotron would cost about $350,000 to $400,000 installed and would cost about $30,000 per year to operate. The availability of reactor time and the associated counting equipment and personnel is highly variable depending on the locale, but there are few programs which have managed to offer routine clinical services for activation analysis. Another recent development is the use of 30 MeV linear accelerators for activation analysis and limited nuclide production. This apparatus can also be used for radiation therapy. More adequate support for such facilities is needed.

The reason for these rather elaborate proposals is that not only do they increase the armamentarium of nuclear medicine but can also achieve significant degrees of dose reduction and with activation analysis can eliminate the need for introduction of radioactive material into the subject.

A similar problem occurs in regard to the availability of short-lived isotopic compounds such as technetium labeled sulfur colloid and albumin. Although some of the larger laboratories can carry out these relatively simple marinades, the laboratory in the busy community hospital is far too busy and limited in pharmaceutical skills to provide these preparations. The national trend in hospital pharmacies is to get away from drug preparation and act simply as a dispensing warehouse. Thus it seems unwise to attempt to develop so highly a specialized capability in the many hospitals throughout the country.

Yet problems of supply and distribution of these services remain. Another purpose of this meeting is to consider ways to provide appropriate facilities and distribution of services. One approach to this aspect would be to set up regional laboratories in major population centers for the very short-lived substances. Such centers could be operated preferably by pharmaceutical concerns under contract with many hospitals and practicing physicians. A number of these special laboratories covering a radius of 100 miles could easily blanket the major population centers of the country.

In regard to the more elaborate facilities some of these may well be located in the larger medical centers so as to provide the very special needs which they offer. This concept is similar to some of the ideas inherent in the regional heart, cancer and stroke programs. In addition to education and the dissemination of information such regional nuclear medicine laboratories would disseminate important services.

MANPOWER

Since it is not possible to reduce radiation dosage without trained personnel, a careful look at this part of the problem is required. The 1966 report of the National Advisory Committee on Radiation (7) focused attention on the relative and increasing shortage of medical and paramedical personnel. Since this report dealt broadly with all ionizing radiation it is not necessary to review the obvious special applications to nuclear medicine.

The problem of giving the medical student and practicing physician some insight into the nature and solutions of radiation hygiene are formidable. Crowded curricula and busy schedules mitigate against a ready acceptance of the vast amount of scientific and technical information necessary for real competence in understanding radiation protection. Additional imaginative methods of presenting such information are needed.

The training of physicians in nuclear medicine has not kept up with the rapid expansion in the demand for these services. In many laboratories this work is handled as a small aspect of an otherwise extremely busy and complicated schedule. Methods in nuclear medicine are comparatively time consuming as compared to those of diagnostic radiology or the clinical laboratory. In most departments of radiology and internal medicine, the image of the chief draws the young physician into many other subspecialties and there is little pressure to provide experience in nuclear medicine. The question of board certification is unresolved at the moment.

On the positive side is the development of training programs for paramedical personnel. There is a surge of activity in radiological and medical nuclear physics throughout this country. These candidates almost always qualify for master or doctoral degrees and acquire board certification. There has been a significant expansion in these programs.

There are now, under development, curricula for the training of technicians in nuclear medicine both at the bachelor and associate level. The latter program has particular appeal to junior colleges and can be carried out in association with many community hospitals.

All of the training programs for paramedical personnel have obtained their major impetus from the NCRH in cooperation with the many interested specialty societies. These efforts may be expected to grow with the expansion of the field.

REGULATION

The field of nuclear medicine has for many obvious reasons had a truly unique experience in regard to regulation as compared to all other specialties in medicine. Under the several Atomic Energy Acts it was recognized that the availability of massive quantities of radioactive material after 1945 required some efforts to protect the public health both on a population and individual basis. Thus medical uses were subject to the same type of restrictions as were reactors. Because of the small beginnings of this specialty this approach was not criticized by the most individualistic profession in the United States and in time the regulation imposed by the AEC came to be very well regarded by those in the active practice of nuclear medicine. The regulations were wisely and compassionately administered by AEC, and it seems to me that most of the pressure to get out of the regulatory business has come from within rather than outside the Commission. It is obvious that in enforcing these regulations that the Government is to some extent engaged in the practice of medicine since they request protocols of diagnostic and therapeutic levels of radiation as given to patients. This information is then used in part to evaluate the application for licensure. They also limit licensure to certain physicians and release certain specified quantities of labeled compounds to any physician for diagnostic purposes only. Certainly it can be said that nuclear medicine has prospered under these restrictions and that the public health has not suffered at least in any measurable way.

The AEC found rather early a peculiar dichotomy in its responsibilities in regulation. In one way it was responsible for accepting certain standards of individual and institutional practice, and in addition it found itself engaged in regulation of radiopharmaceuticals. Although this agency agreed as to its radiological competency it had some reservations about its pharmaceutical qualifications. At the same time the Food and Drug Administration recognizing its lack of radiological competence was not anxious to interfere with a program that seemed to satisfy all of the then current needs. This attitude was formalized by the order of the Commissioner of Food and Drugs (28 F.R. 183, January 8, 1963) exempting all radioactive drugs from FDA control providing that new drugs for investigational use are being shipped in complete conformity with the regulations issued by the AEC. It has been this ruling from which all past and present clinical and research developments have grown.

Nevertheless it is appropriate that a Federal agency regulating drugs do just that, and that an agency which restricts itself to radiation stay in its own field. In this instance the problem is very much the one of King Solomon and the baby (First Book of Kings, Chapter 3, verses 17-28). It is, however, of no importance to the citizen or the patient which Federal agency has this jurisdiction as long as the protection is adequately supplied. The physician is no different than the citizen in this regard. It is probably reasonable to state that up to the present time the medical profession has had no more than the usual differences of opinion with the AEC and in comparison with many other Government agencies probably far fewer

Several months ago in Nucleonics (8-10) there were several articles stating that FDA is preparing to assume its responsibilities for radiopharmaceuticals from the AEC at some time in the near future. These notes raised some concern among investigators for several obvious reasons. They signaled the end of a very simple and rewarding relationship between many groups in nuclear medicine and AEC. They indicated that the clinical investigator in nuclear medicine would then become liable to the same problems that his nonradioactive colleagues have had in regard to forms, records, and approval. Moreover, this change in Federal regulations comes at a time when FDA has been receiving a good bit of attention from certain critics in medicine and the pharmaceutical industry.

There are several aspects of the subject of regulations which are of importance to this conference. The first and simplest concerns itself with development of new standards for short-lived isotopes and similarly labeled compounds prepared in the using laboratory where current practices regarding sterility and pyrogenicity cannot be followed because the compound disintegrates. Many will say that this problem does not exist. My retort is to try it on a lawyer. I believe that one will find that the finer points of astrophysics or Hindu theology are comparatively simple as compared to this one.

The second aspect concerns the involved process of dealing with investigational drugs. Most clinical pharmacologists are somewhat less pleased with this aspect of their work than many of us are in filling out the forms for the AEC. Perhaps our work has been less involved than many others in regard to pharmaceuticals. A more realistic model is that our work is just as involved. If so, one might suggest that the procedures which have been employed so successfully by AEC might be utilized by the FDA not only in the relevant applications to nuclear medicine but also to other nonradioactive drugs.

Another approach of course is to utilize the fact that certain regulations of FDA apply only to interstate shipment of drugs. Recently in Ohio we had the extremely unedifying experience of seeing widespread use of an "anticancer drug" which could only be utilized within the state. The important reason for this restriction was the lack of entanglement with the Federal Government. One might ask at this point just in what position an institution would find itself if it received technetium for chemical purposes and then proceeded to make a safe labeled sulfur colloid for administration to a patient.

The third concern relates to the concepts of FDA in protecting the public from dangerous drugs. There is little argument among reasonable men that the regulatory activities of FDA and AEC have been extremely effective. Certainly more was done for radiation safety after the creation of AEC than had ever been accomplished before. Yet this progress was not solely a function of the regulatory program but rather the product of a multimillion dollar research program involving many Government agencies and universities over the past 25 years.

Similarly progress in protecting the public from drugs was not solely due to efforts of FDA. When anyone becomes involved in this discussion, sooner or later one reads the opinions of Modell. In a recent paper (11) he points out his opinions of mass drug catastrophes as related to science and technology. The effects of potent drugs acting on the central nervous system are no more susceptible to control than are recent civil disturbances in many of our cities. The existence of teratogenic drugs was no more suspected in recent years than was the effect of systemic radium in the late twenties. Thus the ability of governments to regulate all aspects of drugs is no greater than it is in regard to civil rights.

Some of this discussion may seem irrelevant to the reduction of dose from radionuclides. I hope to assure you that it is not so. One may reasonably ask about the doses of drugs or of radiation administered to human beings. For some 25 years I have been engaged in prescribing such doses in conformity with standards of practice within my community and with the best practice and scientific evidence as can be found by research, reading and travel.

In the July 17, 1967, issue of the Hospital Tribune (12), Dr. Herbert L. Ley, Jr., Director of the Bureau of Medicine of FDA states in part "The FDA has not interfered and will not interfere with the right of any physician to express his opinion in scientific publications regarding the use of any drug." Further on he continues "Many of the reports of experimental uses of approved new drugs result from research conducted under an approved investigational new drug (IND) plan. Of course, any physician may, on his own responsibility, administer a drug for an unapproved use or he may increase the dosage in caring for a patient. The physician generally is aware, however, that in any legal case which might ensue, the issue of his liability may turn on whether he followed the drug labeling (package insert) approved by the manufacturer and the FDA or, if the labeling was not followed, on whether he can produce adequate medical justification for his usage of the drug. This is a determination made by the courts, not by FDA." It seems to me that legal responsibility is for malpractice and that malpractice is a local issue decided on the quality of practice in a given case in relationship to scientific evidence and peer judgment. This statement of Dr. Ley may imply liability under Federal law for not following a package insert but this question remains to be tested.

What is surprising and alarming is the presumption that safe radiation dosage and necessary diagnostic information in a given case can be the subject of regulation. The practice of medicine contains no warranty or guarantee except by license and certification. There is no way in which one can return an incorrect diagnosis or treatment as one can a faulty tire or shirt. The physician is entitled to expect a drug of adequate quality either purchased or prepared by himself. The patient can only rely on the physician's integrity to assure his care. These statements place the burden for adequate care solely on the physician; there is no intent to evade responsibility by the physician yet it is not possible to tell the surgeon how far or deep to cut. Thus professional care is at best the exercise of individual judgment.

Another suggestion of Dr. Ley in the above article is that FDA be contacted by letter or by phone if a physician is dissatisfied with a given regulation. This proposal seems inadequate in that it does not provide for public discussion. The reduction of dose from radionuclides and the further development of nuclear medicine are the joint responsibilities of many physians and other scientists, of the pharmaceutical industry, and of responsible government; and all of these problems require wide public debate in scientific conferences such as this one.

Most of these problems could be handled adequately by the formation of a single advisory council both to AEC and FDA. Such a council should consider the joint responsibilities of both agencies so that the practicing physician can minimize his legal obligations and operational expenses and devote his time to patient care.

There is one other aspect of nuclear medicine which requires discussion--that of clinical investigation utilizing radionuclides. There are in a sense two classes of physicians, the clinical investigator conducting formal scientific experiments utilizing human beings and the practioner who is responsible for the medical care of the great majority of our citizens. Both of these categories of physicians at times wish to embark on research studies in man under circumstances which although previously unrestricted now require prior approval of medical review committees. This development poses some serious and perhaps insurmountable obstructions for the development of nuclear medicine.

The principle to be discussed is that, in fact, each procedure performed on a human being, whether it is termed investigative in a formal sense or whether it is classed as diagnostic or therapeutic in a clinical sense is semantically and actually an experiment. The fact that a control or comparison is not specified for each procedure does not alter either the existence of or need for a control. One may not know that there is an available control. Although often the physician cannot state explicitly the hypothesis under test, this statement could usually be made if it were sought.

A professional individual whether a physician, lawyer or man of the cloth is not and cannot be a guarantor of results. The performance of a serological test for syphilis or the therapy of a hangover with aspirin carries a probability of a poor result. Today one finds lawsuits where both the physician and the pharmaceutical manufacturer are sued because of failure of a particular course of therapy. There is no law or ruling of our society which will modify the probabilistic relations of the biological world toward the absolutes so yearned for by legislators and attorneys. Hence no matter how well sanctified a given treatment or test might be the possibility of a deleterious result is always present. Hence the patient may be better served in a difficult situation by submitting to the unimpeded judgment of his single physician.

Another important part of the problem is that of the patient who unwittingly and without apparent benefit to himself finds that he has become a participant in a clinical investigation. These situations have generated a massive and important series of debates involving the conventions of Helsinki, statements of a number of medical societies, the Nuremberg trials and rulings of the Surgeon General of the U.S. Public Health Service. It has been stated that the rights of patients have been grossly breached and that now in each medical center a committee of peers is available to evaluate all clinical research.

One may ask why this problem is of importance to nuclear medicine. As an example recently in our center there were two infants with von Gierke's disease which at present is a uniformly fatal condition. These patients received ^{14}C labeled glucose for study purposes. Both infants eventually died as do all patients with this disease and their courses were unaffected by the isotopic study.

It seemed to me that some type of control would have been desirable in this situation. One type of control might be an animal with normal carbohydrate metabolism. Or perhaps one might elect to use a parent or a sibling or the infant in the next crib. In our institution this problem is currently unresolved and no control observations were made. It is not difficult to determine an appropriate control. Certainly one or two decades earlier this latter study would have been done simply by administering a tracer to some child nearby. Today such action would not be possible unless approved by a committee and it is likely that few committees would have the courage to permit administration of a labeled compound to a normal child solely for investigative purposes, no matter how low the dose.

What is interesting in this discussion are the rights of the individual patient. During the past 2 years we have been exposed to problems of human rights to a greater degree than expected by many, and most of these issues remain unsettled.

Little has been said of the obligations of the sick patient. Our society has no hesitancy in ordering our healthiest and most fit citizens into an environment of 100 to 200 deaths per week and a morbidity rate of over 500 per week. There is no question legally about the obligations of this healthy population. But in medicine for some reasons the situation seems to be reversed. In many cases the volunteer in medicine is really not comparable to the soldier; it is only the patient who is comparable. By our adoption of these current methods of reasoning we tend to block our ability to obtain scientific information of practical as well as of theoretical value. Advances in medicine are often the product of ingenuity under circumstances of great stress and at present the exercise of such ingenuity is impeded. This situation is not dissimilar to the debates of certain academicians of France in the time of Pasteur who thought they were able to decide scientific matters without the need for appropriate experiments (13).

In summary, among the important problems facing nuclear medicine in the next few years are those of new standards for radiopharmaceuticals and the development of adequate regional facilities for biomedical utilization of important new nuclear techniques. Improvement in teaching of nuclear medicine to students and in training for the graduate physician and allied scientists is of concern. Much further consideration needs to be directed to the relations between the clinical investigator and patients in the utilization of labeled compounds. The relationships of the AEC and FDA to the clinical practice of nuclear medicine need further discussion by all groups who are concerned.

This relatively small field is showing very rapid growth and it is providing services to sick people which are truly unique and of great practical value. Its proper development is a great responsibility to all of us.

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FUNCTION OF THE AEC DIVISION OF MATERIALS LICENSING

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The U.S. Atomic Energy Commission's role in the regulation of the medical use of isotopes began on August 2, 1946, when 1 millicurie of ^{14}C was shipped to the Bernard Free Skin and Cancer Hospital in St. Louis, Mo., for research and investigation of the process by which cancer is produced. During the years which have followed, the AEC's role in the regulation of nuclear medicine has grown considerably as has medical use of isotopes itself. We look forward to continued growth in the field of nuclear medicine; however, our regulatory role in this field is unlikely to expand further. During the next few minutes I shall describe the AEC's regulatory program for nuclear medicine as it is today.

The Commission's authority to regulate radioisotope-containing drugs is derived from the Atomic Energy Act of 1954, as amended. Section 161 of the Act provides broad authority for regulation by stating in part, "...In the performance of its functions the Commission is authorized to--

> "b. establish by rule, regulation, or order, such standards and instructions to govern the possession and use of special nuclear material, source material, and byproduct material as the Commission may deem necessary or desirable to promote the common defense and security or to protect health or to minimize danger to life or property; ..."

Section 81 of the Act is more specific to the regulation of byproduct material which includes by far the greatest portion of radioisotopes used in nuclear medicine. The importance Congress placed on the medical uses of isotopes is noted in Section 81 by the statement, "In distributing such material, the Commission shall give preference to applicants proposing to use such material either in the conduct of research and development or in medical therapy."

Under the authority provided by the Act, the Commission has adopted regulations pertaining to the use of atomic energy materials which include radioisotopes used in medicine.

The atomic energy materials which the AEC is authorized to regulate under the Act are source material (natural uranium and natural thorium), special nuclear material (plutonium, uranium, or uranium enriched in the isotope 233 or the isotope 235), and byproduct material (radioisotopes yielded in or made radioactive in the process of utilization of special nuclear material such as might occur in the operation of nuclear reactors). Practically all radioisotopes used in medicine that are regulated by the AEC are byproduct materials. Perhaps of equal interest in the discussions that will take place in this symposium are sources of radiation which are not regulated by the AEC. The AEC does not regulate radium, accelerator produced radioisotopes, or radiation-producing machines such as X-ray machines.

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The AEC operates its regulatory program for nuclear medicine through a system of licensing. Most licenses issued to physicians or hospitals authorize specific radiopharmaceutical procedures.

Any significant changes in the program or additions of new procedures must be reflected by an appropriate change in the authority granted by the license. Institutions with extensive programs for medical research, diagnosis and therapy with radioisotopes need more flexibility than is usually allowed by a specific license, so that operations may be rapidly adjusted to meet new goals as a research and development program progresses or new programs are undertaken. To allow greater flexibility, broad licenses are issued to medical institutions that have extensive competence and are conducting research in the field of nuclear medicine. Considerable latitude is granted by the AEC for use of radioisotopes under the broad license provided that control proposed medical uses of radioisotopes within the institution is under an in-house medical advisory committee, which uses criteria similar to AEC standards for other medical licenses. A general license also has been issued for certain diagnostic uses of radioisotopes. I will discuss this type of license later.

In addition to its licensing program for the control of radioisotope use, the AEC has authority to enter into agreements with State governments whereby the State assumes certain regulatory responsibilities governing the use of radioisotopes, including the regulation of byproduct material in nuclear medicine. To enter into an agreement with the AEC, the State must demonstrate that it has a regulatory program compatible with the AEC's program and that it has appropriate technical capability to operate the program. A part of the agreement is the requirement that both the AEC and the State put forth best efforts to maintain continuing regulatory compatibility. The AEC has so far entered into agreements with 17 States.

The AEC's present regulatory program for the use of radiopharmaceuticals includes considerations of patient safety and drug efficacy as well as radiation safety of the physician, technicians, and members of the public. In general, the requirements for approval of an application for a medical license are that (1) the proposed radiopharmaceutical is one which is safe for the patient and effective for diagnosis, therapy or obtaining desired investigational information; (2) the proposed equipment, facilities, and procedures are appropriate for the effective use of the radiopharmaceuticals and are adequate to protect the health and safety of the patient and the public; and (3) the drugs will be used by physicians whose training and experience in the basic principles of radiation and the clinical use of radioisotopes are sufficient to assure safe and effective use of the drugs.

With respect to the procedures followed to obtain a license for medical uses, a distinction is made between those drugs that are well established and those that are nonroutine or still undergoing investigation. The uses of radiopharmaceuticals which are considered to be well established are those for which the pharmacological and radiological action, preferred route of administration, safety, side effects, contra-indications, dose range, and effectiveness are well known; in general, they have been investigated widely and are used routinely for diagnosis or therapy. There are approximately 36 different diagnostic or therapeutic procedures utilizing 17 isotopes that are, in the opinion of the Commission, safe and effective and satisfactory for routine use. Physicians having proper qualification such as appropriate training and experience, facilities and equipment, and operating procedures are readily approved for these uses.

All other uses of radiopharmaceuticals are considered investigational. Persons proposing to use drugs containing radioisotopes for investigational purposes are required to submit a research protocol that contains information similar to that required by FDA under their investigational drug regulations. The protocol should include among other things, the rationale for conducting the study, the plan of investigation, and outline of related work previously conducted, the number and types of subjects to be studied, radiation dose calculations, and the qualifications of the investigators to conduct the study proposed. After completion of the investigation, the physician is required to submit a report so that it can be determined whether it is appropriate to proceed with further investigations, and if so the manner in which the investigation should proceed.

The Commission relies heavily for assistance in making the evaluations mentioned above from the Advisory Committee on the Medical Uses of Isotopes. The function of this committee is to advise the Commission on policies and standards for regulating and licensing the medical use of radioisotopes in humans. It provides guidance in establishing clinical experience and training requirements for physicians, safety procedures related to medical uses, and criteria for the evaluation of proposals to use radiopharmaceuticals. The members review and provide day-to-day advice on all applications received by the Commission for the use of radiopharmaceuticals undergoing investigation. The committee currently consists of 10 members: seven physicians, two medical physicists, and a pharmacologist.

Three AEC regulations that apply to nuclear medicine are 10 CFR 20, "Standards for Protection Against Radiation," 10 CFR 30, "Rules of General Applicability to Licensing Byproduct Materials," and 10 CFR 35, "Human Uses of Byproduct Material." The provisions of 10 CFR 20 pertain primarily to radiation safety and contain the standards and requirements for protecting the licensee and the public against radiation hazards; 10 CFR 30 prescribes general rules governing the AEC licensing program for byproduct material; and 10 CFR 35 contains the criteria for licensing persons to receive, possess, and use byproduct material in humans.

Dr. King, the next speaker, is a member of the Advisory Committee on the Medical Uses of Isotopes. He will discuss in more detail those aspects of the program related to patient safety, drug efficacy, and physician qualifications. I would like to review our regulatory policies as they apply to the health physics aspects of nuclear medicine; that is, to control the exposure of physicians, technicians, nurses, and the public incidental to the practice of nuclear medicine. I understand that this is an important consideration of this symposium.

As applied to the practice of nuclear medicine, the standards for protection against radiation set forth in 10 CFR 20 are designed to control the radiation exposure received by physicians, technicians, and members of the public during the use of radioisotopes. They do not apply to the radiation exposure of patients who are administered radioactive drugs for purposes of medical investigations, diagnosis, or therapy. The standards contain many specific requirements such as those for surveys, personnel monitoring, and waste disposal which are intended to lead to control of radiation exposure; however, more germane to the discussions which will take place during this symposium is the manner in which the basic exposure limits contained in the standards are applied. These limits are derived from the recommendations of the ICRP and NCRP for permissible exposure of radiation workers and individual members of the public. In making their recommendations for permissible dose, the ICRP notes that any exposure to radiation is assumed to entail a risk of deleterious effects. ICRP goes further, however, to note that the quantitative relationship between dose and risk is not well known, but that maximum permissible doses can be set so that there is a low probability of radiation injury without undue restriction of the benefits of ionizing radiation.

Two views of the ICRP applied to the exposure of radiation workers within the framework of 10 CFR 20 are: (1) applications for licenses are examined to determine that the exposure of radiation workers is minimized since any exposure to radiation is assumed to entail a risk of deleterious effects. Efforts to minimize exposure must be compatible with achieving the objectives of the procedure and accomplishing them without undue sacrifice of time, money or quality of results; and (2) no attempt is made to weigh the benefits which might be derived from the use of any specific radioisotopic procedure against the risk of deleterious effect to the radiation worker when operating within the exposure limits. Any attempt to place a quantitative value on exposure to the radiation worker, when operating within applicable limits and relate this value to the benefits derived by the worker, is an exercise that is probably not very meaningful. In medical applications, a primary consideration must be that the patient's interest is paramount; that is, a procedure which minimizes risk to technicians at the cost of compromising the medical value of the procedure to the patient would be considered unacceptable; therefore, an applicant is free to choose radioisotopes and follow the radioisotopic procedure which he believes will best serve his purpose even if his choice might result in a slightly higher dose to radiation workers. All such exposures must of course remain within the limits set by 10 CFR 20.

The exposure of radiation workers in the practice of nuclear medicine, at least those subject to AEC regulatory jurisdiction, appears to be well controlled. There are 2,153 medical licensees subject to AEC jurisdiction in addition to another 1,700 under Agreement State jurisdiction. During the calendar years of 1965 and 1966 and up through the first calendar quarter of 1967, a total of 14 exposures in excess of applicable limits was reported by AEC licensees to the Commission. These exposures range from slightly in excess of the whole-body exposure limit of 1.25 rem in a calendar quarter to 15 rem in a calendar quarter. Most of the reports attributed exposures to the use of X-ray machines, fluoroscopes, or radium, with very little of the exposure coming from byproduct or accelerator-produced materials. During this same period the AEC conducted over 1,000 inspections of medical licensees. Information gathered during these inspections and information supplied by three major film badge companies would indicate that the annual exposure to persons engaged in the practice of nuclear medicine is well within applicable limits. Over 95 percent of those engaged in nuclear medicine receive less than 1 rem per year and over 98 percent receive less than 2 rems per year.

My remarks over the past few minutes have been concerned with the AEC regulatory program as it is today. I would now like to make some general comments about the AEC's long-range policies concerning its eventual role in the regulation of nuclear medicine. As the use of radiopharmaceuticals has become more widespread and better understood, many of the regulatory controls exercised in the early part of the program are no longer necessary and others which are currently in effect may become less important. We believe that, to the extent possible, radiopharmaceuticals should eventually be regulated in a manner similar to other drugs, and in the past few years the AEC has undertaken some changes in its regulatory requirements which lead toward this goal.

In 1965 the Commission changed its regulations to authorize the use of small quantities of radiopharmaceuticals for specified diagnostic purposes under a general license. These include ^{131}I for the measurement of thyroid uptake and blood and blood plasma determinations, ^{125}I for blood and blood plasma determinations,

^{58}Co and ^{60}Co for measurement of intestinal absorption of cyanocobalamine, and ^{51}Cr for determination of red blood cell volumes and studies of red blood cell survival time. Under the general license it is necessary for the physician to register with the Commission prior to receiving the radiopharmaceutical, but he does not submit an application for a license. This means that it is not necessary for him to provide specific information about his qualifications. The quantities of radioisotopes which a physician may possess under a general license are small so that little radiation hazard to employees or the public exists. These drugs may not be administered to a woman known to be pregnant nor to a person under 18 years of age. The supplier who distributes radiopharmaceuticals to general licensees must be licensed by the AEC to do so and must also hold an effective new drug application from the FDA for the drug; or in the case of a biologic he must hold a license issued by the Secretary, Department of Health, Education, and Welfare.

We believe that the medical general license is a step in the direction of placing the use of radiopharmaceuticals by physicians on the same basis as the use of other pharmaceuticals. The radiopharmaceutical procedures authorized under the general license have been in use for many years and are well known. Physicians have ready access to information about the procedures in published literature, and the package inserts that accompany the drug when distributed under authority granted by FDA or HEW provide information related to effective use of the drug. The AEC is following utilization of radiopharmaceuticals under the general license to determine its effectiveness and to determine whether it will be possible to expand its scope.

Another regulatory change affecting nuclear medicine that is currently under consideration is more administrative in nature. It is designed to simplify the licensing process both for the Commission and for applicants. Most diagnostic uses of byproduct material can be divided into two groups based on similarity of licensing requirements. Group I includes the diagnostic uses characterized as uptake, dilution, and excretion studies. Group II consists entirely of scanning and tumor localization procedures.

It has been the general practice of the Commission to issue licenses only for the uses, quantities, and types of byproduct material requested even though a physician obviously might be qualified for a license of greater latitude. Under a recently proposed rule change, if a physician applies for a single diagnostic procedure within a group and if he is qualified for all the diagnostic procedures within a group, he will be licensed accordingly. It is hoped that this change, if it is adopted, will significantly reduce the number of applications a physician currently finds necessary to submit to the Commission as his nuclear medicine program develops.

Several policies are guiding the AEC in making changes in its program for the regulation of nuclear medicine. As mentioned earlier, the present AEC regulatory role includes considerations of patient safety, drug efficacy, and physician qualifications to practice nuclear medicine, as well as radiation safety of employees and the public during manufacture and use of the drug. We believe that eventually the regulation or other controls applied to radiopharmaceuticals and to the practice of nuclear medicine should be as follows:

1. Radiopharmaceuticals should be regulated on much the same basis as other drugs by Government agencies that presently have similar responsibility for nonradioactive drugs.

2. Physician qualifications to practice nuclear medicine should be established and controlled by the medical community itself or by State and local examination boards that make similar judgments in other fields of medicine.

3. The AEC should limit its role in the regulation of nuclear medicine to considerations which govern the radiation safety of employees and the public during the manufacture and the use of the drug as is currently the AEC role in other uses of byproduct material.

Future changes which might occur in the regulatory program will be made with these long-range goals in mind. Since the problems are complex it is unlikely that all these goals will be achieved soon and probably not in one step; however, we will continue to work closely with other regulatory agencies and seek the advice and cooperation of the medical community to reach these objectives.

FUNCTION OF THE AEC ADVISORY COMMITTEE

E. Richard King, M.D.[1]

I am representing a committee called the Advisory Committee on Medical Uses of Isotopes. As Mr. Cunningham has told you, there are 10 members of the committee, seven of whom are physicians--but these physicians are not all practicing physicians. Two of them are really biochemists, and the other five represent specialties that are about as varied as you can find. Since I am to speak in their behalf, and especially after Mr. Cunningham has told you that the AEC has a complex problem, I would like you to meet with this committee sometime; then you would really learn what complexity is. Naturally we don't agree on everything, but occasionally we do agree.

The committee to advise the AEC dates back to 1948 when the Advisory Committee on Isotope Distribution was appointed. This was divided into two subcommittees. One was a Subcommittee on Human Applications, which Marshall Brucer immediately and very affectionately labeled the Subhuman Committee; the other was a Subcommittee on General Application. In 1959 the Advisory Committee on Isotope Distribution was dissolved and the present Advisory Committee on Medical Uses of Isotopes was formed.

The function of this committee is to advise the AEC upon their request. We are asked to advise them on various problems with which they are confronted, but I'm sure that they have a lot of problems on which they don't request our advice. Our function is to advise the AEC in the development of standards of criteria for protection·relative to the regulation and licensing of the use of radioisotopes in humans. Of course we are restricted only to those applications involving humans or in those pertaining to biological studies.

I'm going to read our principal duties, which I received from the Main Office, and I think these duties outline the scope very well.

We review and comment on applications that request authorization to use radiopharmaceuticals as investigational drugs. (I'll go into a little detail on that later.) We review the reports and the published literature about investigational drugs to advise--and this word "advise" is prevalent, and it should be--on the safety of continuing further investigations. Also, we review the extent to which the investigations establish the safety and efficacy of the drug for routine use. (I'll speak briefly on these two words, "safety" and "efficacy.") We identify areas where further investigations are needed to establish the safety and efficacy of drugs for routine use. We provide advice about special licensing procedures and requirements which might be appropriate for certain routine uses of radiopharmaceuticals. We comment on proposed regulations that govern the use of radioisotopes in humans. And lastly, we provide advice in establishing certain medical licensing criteria, such as training and experience requirements for physicians, protocol requirements of investigational drugs, and so forth.

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At the present time the way we go about this is to review certain applications that are forwarded to us from the headquarters office (applications for licensure). Many of these applications are for radionuclides for animal use. In addition, our committee reviews applications for teletherapy devices and for sealed sources used in therapy. Of course the teletherapy devices and the sealed sources are really substitutes or replacements for X-ray generating devices, radium, or radon. Ordinarily they are not thought of as coming under the definition of nuclear medicine.

At stated intervals we also recommend to the headquarters office (the Division of Materials Licensing) when the clinical use of radiopharmaceuticals can become routinely licensed. We do this, again, on request. When we meet annually (or more often) usually the group from the Division of Materials Licensing presents applications for certain isotopes or labeled compounds, asking if we think there has been enough experience with it, or the evaluation is complete, so that such compounds and isotopes can be released for routine clinical use. As I indicated before, we meet with the people from the headquarters office at least annually.

The 10 members of our committee are located all over the country and we are all connected, in one way or other, with academic institutions. This means that we are all on the road a part of the time. I think the headquarters office really displays the patience of Job to put up with us sometimes. This also means that many reviews are late. When I came back a week ago today from 2 weeks of vacation, I had a stack of applications on my desk that was over 12 inches high.

Telephone consultations usually cover something of a very unusual nature. As you know, the investigational use of drugs, including radiopharmaceuticals, is in three phases, and usually with Phase II, where a small number of patients are going to be studied with a compound which has a label, we are consulted by telephone. This small number of patients may be a group of two or three patients with a very rare disease. The investigators have a new compound they want to evaluate, and it has a radionuclide label. Maybe we have had their application for 2 or 3 weeks, and it hasn't had a chance to go through the entire committee, or they may get a patient with one of the rare diseases, and he's dying.

We are also asked to evaluate safety procedures relative to the medical uses of isotopes. Here quite often the problem, at least in the last 2 or 3 years, involves generators. This as far as the committee is concerned is primarily a problem of drug safety and/or efficacy. As Mr. Cunningham told you, his office takes care of most of the health physics problems relative to the exposure to both the user and the bystander. The radiation exposure to the patient is a problem with which our committee is asked to help.

When we review these applications for nonroutine and/or investigational uses of isotopes, one of the things we scrutinize is the dosimetry calculations. Again I'm speaking for the whole committee and not just for myself. We have two physicists on the committee who are authorities on dosimetry, and while the remainder of us on the committee many times do go through dosimetry calculations, we usually depend on the two physicists for the final check as to whether the dosimetry is correctly portrayed. I know that many of you--and certainly many of the people with specific licenses on the outside--wonder why we put this emphasis on dosimetry. I remind you that we're speaking here of radiopharmaceuticals that are under investigation and that are nonroutinely used. This would probably be the Phase III studies. We feel in a situation like this that the investigator should at least know how to do the dosimetry if he wants to use the isotope in humans.

Many times we get applications for the Phase III type of use in which the dosimetry calculations are not only copied, but they are actually photostated from a radiopharmaceutical brochure. It's quite likely that the applicant doesn't know how to do the basic dosimetry calculations, so we return the application and ask him to do his own calculations. He doesn't have to do them himself--this is understood--he can have a physicist do them for him if he has one available.

We do not evaluate the laboratory and equipment from a safety standpoint. This is again a health physics chore that is carried out by headquarters office. We do try to evaluate the training and experience of the user. I remind you we are not talking about routine uses, we are talking about the nonroutine and/or investigational uses.

For teletherapy equipment we require a little more detail on training and experience than we do for the routine applications for nuclear medicine.

Insofar as drug safety and efficacy are concerned, these are items which our committee has been giving a little more emphasis in the past 2 or 3 years than previously. An example of drug safety is probably the generator. As Dr. Saenger told you, most of the new labeled compounds that have been developed were developments of the hospital, the medical school, or the research lab, and not the pharmaceutical house. This means that the basic research on these compounds and the early human studies of toxicity and metabolism, and so forth, and then the limited human evaluation has to be accomplished with compounds prepared in the laboratory. Sometimes this worries us a little bit as we wonder whether the individual, who is doing this work, is looking into pyrogenicity, toxicity, and other aspects of drug safety for the compound that he is synthesizing. This is really the only place where we are involved with generator problems because, as I said before, the health physics of generator problems is taken care of by the headquarter's office.

I must say here that if a compound, such as we're speaking of, is developed by the pharmaceutical house, we really don't worry too much about it (no more than we would worry if we were taking some of the aspirin that Dr. Saenger was talking about for hangovers) or whether it is pure, has pyrogens, and so forth. But with the compounds developed in the laboratory--and since the day of generators is with us, and we're making all kinds of compounds out of everything from technetium on up and down--drug safety may become a problem.

In evaluation of an investigational use, we do require a research protocol which is a routine protocol. This protocol is available from the headquarter's office and was developed by the committee. A portion of this protocol involves informed consent of the patient.

In closing, I would like to say, again speaking for the committee, that I don't think any of us would be very unhappy if a situation should develop whereby the medical profession could take care of this type of work itself and the committee could be dissolved.

ROLE OF NCRH IN NUCLEAR MEDICINE

Raymond T. Moore, M.D.[1]

It is deeply gratifying to me to be a part of this symposium and to be able to discuss with you the emerging role of the National Center for Radiological Health in nuclear medicine.

The Public Health Service has been active in varying degrees in many aspects of the Nation's medical research and care as well as preventive public health services. The activities of the Public Health Service are related not only to clinical and basic research but also to problems arising from man's exposure to his environment. Radiation exposure is a part of the world in which we live, whether it be from natural background radiation, fallout from atomic explosions, medical and dental X rays, or exposures to radioisotopes.

First let me acquaint you with the National Center for Radiological Health and its place within the Public Health Service. The recent reorganization of the PHS, completed on January 1, 1967, resulted in the creation of five operating Bureaus. These are:

1. The Bureau of Health Manpower, a new Bureau addressed to the problem of providing adequate resources of medical manpower.
2. The National Institutes of Health, the basic research arm of the Public Health Service.
3. The Bureau of Health Services, emphasizing direct medical care programs.
4. The National Institute of Mental Health.
5. The Bureau of Disease Prevention and Environmental Control.

This latter Bureau, emphasizing the classical preventive public health programs, encompasses five operating Centers of which the National Center for Radiological Health is one. The other Centers are:

1. The National Communicable Disease Center.
2. The National Center for Chronic Disease Control.
3. The National Center for Air Pollution Control.
4. The National Center for Urban and Industrial Health.

The primary activities of the National Center for Radiological Health may be described as:

(1) investigation, surveillance and studies of radioactive contamination and other radiation hazards in the environment,

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(2) research and development in radiobiological effects and radiation exposure reduction and control methods,
(3) training of specialists in the radiological health field,
(4) technical assistance to State and local governments and other organizations, and
(5) dissemination of information.

Probably the greatest contribution to development of the National Center for Radiological Health resulted when the Surgeon General established the National Advisory Committee on Radiation in 1958 to provide guidance in matters pertaining to the control of radiation hazards in the United States. This Committee has served you for the past 9 years and has provided three reports which presently are available to you.

The National Advisory Committee on Radiation in its latest report to the Surgeon General, dated April 1966, established a definition which can be used in our discussions of nuclear medicine. It is defined as that branch of the radiological health sciences which pertains to the application of radioactive materials to the diagnosis and therapy of disease and to the study of physiological processes in man. The Committee also estimated that the use of radioisotopes in medicine was growing at the rate of at least 15 percent per year.

The increasing clinical use of radiation in many forms, growing industrial use of ionizing radiation, and the development of more practical uses in consumer products, has placed considerable pressure on the NCRH to move ahead in this field. It prompted us to plan and convene this conference in accordance with our overall mission which is to "plan, conduct, coordinate, and support a national program for prevention and control of radiological hazards to public health."

In order for us to move forward in an understanding of the radiological hazards, potential and inherent, in the burgeoning disciplines of nuclear medicine, we must first try to identify possible problem areas. These will certainly include medical judgment and clinical use, research, and manpower considerations.

The use of radioisotopes in a clinical setting presents interdependent problems such as: control of radiation exposure received by those caring for the patient whether occupationally or from contamination, and control of radiation received by the patient from intentional exposure--in this instance a patient is deemed to derive a direct benefit.

Thus we are interested in nuclear medicine because this involves the exposure of humans to radiation and we feel that this exposure should be as minimal as possible commensurate with the benefits to be derived. The benefit versus risk judgment must always be made and the expected benefit should ideally always be equal to or greater than the risk involved.

The Center has no authority to establish regulatory standards. It can, however, provide recommendations which States and other public and private organizations may utilize. We may also assist other organizations through research and development of their standards. The original Division of Radiological Health as well as its successor, the NCRH, has supported intramurally research related to the control of radiation hazards. The research activities include.

(1) determining through various experimental and epidemiological methods the effect of radiation on man, and
(2) developing methods for reducing and controlling radiation exposure to man.

The practical opportunities to reduce radiation exposure are far greater in diagnostic radiation procedures than in any other field of medical radiation use. The public is largely unaware of the risk entailed and even less aware of the opportunities to reduce them. One of the basic missions of the Public Health Service is to identify potential risk to health, aid in the development of techniques to reduce this risk, and to inform the public. This is done in the context that the patients' needs are paramount and there should not be over- or underutilization of any diagnostic procedure.

The NCRH has made some contributions in this field already. In 1964 the Division of Radiological Health called a conference at the University of Chicago to consider the "medical uses of radium and radium substitutes." The conclusions of this conference are in a report that is available upon request.

Following the conference we began to plan in earnest our efforts in nuclear medicine. A start was made in 1965 and now in 1967 we have been able to support at least one identifiable unit of this discipline. This unit investigating clinical aspects of nuclear medicine is located at the University of Cincinnati. This is a modest beginning and we are pursuing three major areas of identification. Briefly these are:

(1) Direct clinical applications of new and promising pharmaceutical procedures, thus attempting to bridge the gap between research advances and clinical practices.
(2) Radiopharmaceutical and instrumentation development for improved diagnoses utilizing the least possible dose. One of the methods for reducing the radiation dose to the body is the utilization of short-lived isotopes tagged to compounds having a short biological half-life.
(3) Development of techniques to assess accurately the dosimitry of radiopharmaceuticals.

It is not possible to use radiopharmaceuticals _in vivo_ without the organ or organism receiving some absorbed dose. We have a continuing effort to determine dose-radiation relationships of importance to man. I call your attention to the Summary Report on Radiological Health Research, which is also available upon request. At the request of the Society of Nuclear Medicine and the National Center for Radiological Health, the Stanford Research Institute is currently conducting a national survey to determine the magnitude of the use of radioactive material in nuclear medicine. This survey is designed to establish a baseline from which the trends in nuclear medicine can be followed and to get sufficient data to estimate radiation exposure to the general population from nuclear medicine procedures. The current data are made available for your consideration and possible further discussion during the working sessions of this meeting.

Now let us turn our attention to nuclear medicine manpower questions. We are not alone in feeling that much more needs to be done to provide the trained physicians, professional assistants such as physicists, and nuclear medicine technicians. The American College of Radiology, the American Society of Clinical Pathologists, and the Society of Nuclear Medicine all have committees concerned with training in nuclear medicine.

In addition there are the nuclear medicine technician registration programs of the American Registry of Radiologic Technologists, the American Association of Medical Technologists, and proposed similar registration sponsored by the Society of Nuclear Medicine.

The AEC and the Agreement States are specifically concerned with minimum preparatory training of physicians as a basis for receiving a license to purchase and use radiopharmaceuticals in medical practice.

The NCRH is concerned with the whole nuclear medicine system and therefore the adequacy of all members of the medical team. This is in keeping with our goal to help provide an adequate number of qualified personnel to meet the manpower demands of the total national radiological health efforts.

Two means to accomplish this goal are used. The first is to provide highly specialized technical training for Federal, State, and local personnel on an immediate basis for rapidly expanding radiological health programs requiring multidiscipline personnel. The second is to support and design training activities through existing educational institutions which will permit an orderly growth and development of formal educational programs that are adequate for meeting future radiological health needs.

For purposes of our meeting here at this great university I would like to comment only on the nuclear medicine manpower problem as it relates to the training of nuclear medicine technologists. I think you are all aware that by and large the physician interprets the information that is developed by technologists.

We could ask the question, "Who are and where do these technologists come from?"

Instead let us think a few moments on the value of a well-trained technologist to the laboratory that strives for excellence in their procedures. You know the sequence of events--a patient is referred to the laboratory for the purpose of having a laboratory procedure performed. The patient may be interviewed by a staff physician in the lab who confirms that the requested procedure is indicated. At this point the patient may be put into the hands of the technologist who performs the test from start to finish; thus, the technologist has the responsibility for the diagnostic value of the information which the staff physician interprets in reports to the referring physician.

As you know there is a shortage of qualified nuclear medicine technicians. While the Public Health Service has a strong obligation to assist in fulfilling these needs, it is not conceived that it is a basic function of the Radiological Health Center to meet the overall shortage of personnel in this field, but that we should endeavor and assist in the following areas:

(1) We should be a participant in developing curricula for these professions and subprofessions which encompass and integrate good radiological health practice. This will necessitate setting up pilot studies of curriculum development and granting of funds to test these curricula.

(2) We should participate in the development of uniform criteria for certification of these professions and subprofessions. These criteria apply to radiological health matters.

(3) We should develop criteria of approval based on good radiation practice for the facilities and radionuclide handling equipment associated with these professions.

(4) We should develop model legislation and regulations and assist the States in designing and implementing State radiological health programs pertinent to these professions.

We can report that the NCRH is now supporting the establishment of a prototype 2-year course of study leading to the B.S. degree in Medical Technology, with a Nuclear Medicine option at the University of Cincinnati. On completion of this program candidates are eligible for taking the nuclear medicine technologist registration examination given by the American Association of Medical Technologists; however, enrollment is not limited to degree candidates. Qualified persons in nursing, medical technology, and X-ray technology are also eligible to receive the 12 months training conducted in the radioisotope laboratory. The Center is actively exploring other avenues for developing well-qualified personnel and these will be no doubt explored in a working session.

Let me reiterate three points--radiation protection practices and contamination control are only as successful as the personnel involved make them; better trained staff including physicians and technicians will result in fewer retests and preventing unnecessary exposure to the patient as well; and the nuclear medicine technician holds the key to the success of any diagnostic test.

In summary, the National Center for Radiological Health, as I know each of you is aware, is vitally interested in nuclear medicine. The trend of our activities is toward the development of new methods leading to the reduction of unprofitable exposure in whatever way seems appropriate as well as toward better medical care through more efficient use of radiation. We must always keep in mind that the patient should derive a real benefit from every procedure and yet be protected from the potential hazard inherent in the purposeful exposure to radiation.

DISCUSSION

Dr. Harper:

I'd like to ask Mr. Cunningham: What is the origin of the legal limit, 30 millicuries, with which you are permitted to let a patient leave a hospital. Could you discuss this a little bit?

Mr. Cunningham:

I could bypass that question by saying that it's before my time, but this is not right.

Dr. Harper:

You're not responsible for it then; you're safe.

Mr. Cunningham:

No, I am responsible. There is no legal limit, as such; this is a criterion that is used. Well, it is established in our Medical Licensing Guide; but there is no legal requirement that a person with greater than 30 millicuries be restricted to a hospital. It is just a reasonable dividing point. If there are any reasons why you can release a patient with greater than 30 millicuries, depending upon the situation at home and not tie up a hospital bed that might otherwise be necessary, there is no objection to releasing them. It is just a criterion to follow.

Mr. Harris:

Mr. Cunningham, for information only, is this 30-millicurie limit for a specific radionuclide or is it a general limit? I'm showing my ignorance, but I don't mind.

Mr. Cunningham:

The limit was first developed when there weren't too many radionuclides available except ^{131}I and I guess some ^{60}Co for implants, and perhaps some ^{192}Ir. We haven't done much with that, and perhaps we should come out with new criteria, but it is just a guideline and not a requirement.

Dr. Harper:

Excuse me. One of the purposes of this meeting might be to discuss your guidelines in terms of the fact that there's a lot of external difference between 30 millicuries of ^{55}Fe and 30 millicuries of ^{60}Co or ^{51}Cr for example. This might be one of our valuable functions here, at this time, to think about these things.

Dr. Hilberg:

Yes, I think this is certainly appropriate for one of the working groups, and the question should be explored.

Dr. Saenger:

I would like to ask Mr. Cunningham--perhaps I didn't understand it, Dick--you said that the Commission wants to avoid this judgment of benefit versus risk; is that in terms of the worker?

Mr. Cunningham:

Only in terms of the worker. I was discussing radiation exposure of the worker.

Dr. Saenger:

Then you also talked about 14 exposures above certain limits and so on; this was also in relation to the worker? Not in relation to the patient?

Mr. Cunningham.

That was in relation to the worker, the worker only.

Dr. Ross:

We have heard about the provision of training for paramedical personnel, which is certainly very important in the United States, but recently I was privileged to participate in a worldwide survey of the development of nuclear medicine in what euphemistically might be called the developing countries. The greatest need, expressed uniformly by these gentlemen in various countries, is the tremendous lack of any paramedical personnel to support them in what they are doing. They themselves are really not prepared to train such individuals, but from observation their effectiveness would be tremendously increased if they had good paramedical people who could come in and do just what was described.

Is it possible that the United States, through the organization which Dr Moore described in Cincinnati, would be prepared to provide training for paramedical personnel who may come from Africa or from Asia? If you are able to provide such training, is it possible that you are able to provide any financial support for such people who might enroll in such programs?

Dr. Moore.

I'll only tackle part of this. At our National Center, the answer is no we cannot. Politically, this is foreign aid; in that context, we do not provide it.

Now, I'm not speaking to any facilities at the University of Cincinnati or any other university for providing training, but this is not something that we can do right now.

I will turn it around a little bit and say we are working with--and this is a very minor amount--the Pan American people in trying, upon request, to advise them of factors about radiological health programs in developing countries, but this is very meager and I wouldn t want to mislead you about it.

Mr. Harris:

I would like to inquire a little more--back to Dr. Moore--about this training of paramedical personnel, and of whom do we speak?

Frankly, I think that in this country there is a dearth of input of people with an engineering background. Engineering schools apparently behave as though they had never heard of nuclear medicine, with basically trained chemists, who might later become nuclear chemists, or with people with similar or related interests. There seems to be essentially no communication between that world and ours, and I think the need in our country is just as acute as those in the developing nations. Now, how does the Cincinnati effort and the NCRH effort stack up in terms of this?

Dr. Moore:

First, the need is there and I wouldn't attempt to tell you it isn't. We define paramedical personnel as those people who are not physicians--this is just my definition--who are necessary aides so that the physician can do his work.

The effort in Cincinnati (and I probably should let Mr. Simmons or Dr. Saenger mention it) is frankly a pilot effort to see what we can do there, to find if we can develop a curriculum, to see if we can hook this training in nuclear medicine into an educational system where students get a B.S. degree, or some other degree.

I'm sure all of you are acquainted with the developing junior college system in this country, and these schools are in the training field. They tell us "We can train paramedical people; you just tell us what they need to know." This is a real question, trying to come to an agreement on what they need to know. This is true not only in nuclear medicine but in other fields. We need a curriculum that we can bring to you and say, "The nuclear medicine technologist should know this." Frankly, we don't have one that would stand up, but we are trying to assist in developing one.

I offer this as a partial answer to your question, but this is the area in which we are working. I believe Dr. Saenger could probably comment more specifically.

Dr. Saenger:

Well, I think there are several lessons that we have learned so far. Our original program started out as a training program under the National Institute of General Medical Sciences where we have trained radiological physicists--to a doctoral degree. As the Division of Radiological Health, now the NCRH, got into the program, this was broadened somewhat. We have taken men from nuclear engineering and from environmental health and have trained them also for a degree. I think it is very important that these people just don't come in and kind of rattle around for a year or so, sort of nibbling in the laboratory, but that they work for specific degrees.

After these two programs got to the point of turning out finished people--then under Mr. Simmons' direction (Mr. Simmons is here, he could speak on the course content) the program was then broadened to try to certify the laboratory technician and the nuclear medicine technician. This placed us into a simply ghastly situation--as far as I am concerned--with the question of who certifies these people and which certifying board. The medical technologist group are into it up to their armpits. Of course I don't know that we've really heard from the X-ray technicians as yet. Then the Society of Nuclear Medicine is very much concerned, as they should rightly be, because I guess that group uses these people more than anyone else. But the question of how you certify the individual, once they have the academic degree, is going to be a very critical one because each one is going to play the game a little bit differently, and I know this causes Mr. Arve Dahl tremendous agony, soul searching, and things of this sort.

I think again the critical point here is that the individual attains a degree. As far as the junior college is concerned, or the 2-year accreditation or certification, or associate degree--or whatever it is they get--we do not have a program of this sort in operation. We do have a course content approved by our university and we are now going to have one of these community colleges (this is being built right now), and we hope to have such a program.

Mr. Simmons has been developing a curriculum for the 4-year candidate. Subsequently we hope he will develop one for a 2-year candidate. This about covers everybody except the high school graduates, and so on. We have, for example, a young fellow in our laboratory who had 2 years at a college in Newburgh, N.Y., and there he learned how to maintain instruments and do essentially, I guess, what you call meter reading, meter jockeying, and so on. He goes around and does surveying all over the university, and he's really a very capable fellow, within limits. He can talk to doctors tactfully (which always surprises me), and yet he had a 2-year training. I've met a couple of other fellows of this type who have worked for the State of New York in a center that Mr. Trollenburg runs in Albany, and they have had this 2-year training and they are really technically extremely competent. They can do a great deal of this groundwork which none of us really like to do. I think if this is extended to the field of nuclear medicine it would be of great value.

We have a couple of people in the laboratory whom we just kind of picked up off the street, and they can do routine tasks. You never really feel thay have had any solid academic training so that you can turn over jobs, such as letting them administer tracer doses of 1 microcurie or something like that. It scares me when we think of things like that. They can sit there and watch the scanners run and things of this sort, but they don't really have enough competence to leave them alone with a patient. I think this is the point at which the curriculum which we are trying to develop (and I'm sure there are many other people trying to develop) will be of value because then you can take a junior college in almost any community and have them work with a good clinical laboratory (much as we have trained most of the X-ray technicians around the country) and get a great many people to do the type of work for which we have a need.

Dr. Hilberg:

Before I call on anyone else, I would like to identify the Arve Dahl referred to. Mr. Dahl is the Chief of the Training and Manpower Program of the National Center for Radiological Health.

Dr. Kuhl:

I think that we certainly need a diversity of talents in paramedical personnel in nuclear medicine, and I am sure that a 4-year college education should give us people who are better trained than our present technicians, most of whom only have 2 years of college. But I wonder if one of the problems we are addressing ourselves to is the shortage of nuclear medicine technologists, or whether the 4-year college program requirement would help us at all in this regard. I think that perhaps it would provide us, in an individual department, with one well-trained individual who might be a chief technologist, but I can't imagine that it would provide us with enough people to do all of the nuclear medical technology work in the department. I offer as a possibility that the trouble with the current 2-year program is that it is laced with service obligations rather than with education and if we addressed ourselves to an appropriate 2-year training of a nuclear medical technologist we might end up with a better trained person and more people at the same time.

Dr. Beierwaltes:

Dr. Moore, I think that we have something that would be very helpful to you and that you could participate in with regard to training nuclear medicine technologists. A very significant event, I think, happened about a year ago, and unfortunately very few people know about it. When I was President of the Society of Nuclear Medicine we asked for an audience with Nick Taylor, the Secretary of the Division on Education of the AMA, because we knew that the AMA had been approached by several different groups. He's interested in a program of training and certifying technicians, and we wondered if it would be helpful to them to have everybody agree on a program, a curriculum, and a method of inspecting the schools and certifying them. They said this would be very helpful. So they called a meeting, and attending this meeting were the designated representatives of the Society of Nuclear Medicine, the American College of Clinical Pathology, the American College of Radiology, and the two or three interested and well-recognized technician societies. So to the best of my knowledge everyone that was interested in this problem was officially represented there.

Each group was asked to bring any curriculum they had for nuclear medicine technicians to that meeting, and also the format on credentials, admission to schools, what schools should do the training, and so forth. We started out with the topic of curriculum, and within an hour we were amazed at how almost exactly all the interested groups had come up with almost identically the same curriculum. With Nick Taylor's excellent guidance we merely changed a few words here and there and within an hour had complete agreement on what the curriculum should be for the training of nuclear medicine technicians.

Secondly, we went to the educational background requirements, the location of junior colleges, length of the curriculum, what prerequisites would be acceptable, and so forth, and we also had complete agreement on those within another hour.

When we left that meeting there was agreement among the representatives present which would be taken back to the individual societies for appointment of an inspecting board for the AMA, to inspect actual schools that would be started with this curriculum, credentials, and so forth, in mind.

There has been continued discussion and there has been no disagreement on it. The problem is that it has been very difficult for these five groups to actually approach their societies and get the designated representatives, and so forth. But hopefully the Society of Nuclear Medicine is bringing that to pass during this coming year.

Where your group might help out a great deal without any strain or stress of long-involved negotiations or anything, is to approach Nick Taylor. If he doesn't have the information, then contact Irv Kaplan from the Society of Nuclear Medicine who will have it. They have the approved curriculum, the prerequisites, the duration of training, and so forth.

Dr. Moore:

Is there a report yet?

Dr. Beierwaltes:

No, I don't think there was any particular report. We just all agreed on it. I would imagine that Nick Taylor does have the minutes of the meeting with the approved curriculum.

Dr. Hilberg:

Mr. Dahl has been in touch with Nick Taylor and they have corresponded extensively, have met together and so on, and are working together on this particular thing.

Dr. Saenger:

Mr. Guy Simmons is using the curriculum. He has been using the curriculum they recommended for a year now. He received it right away.

Dr. Moore:

I'd like to point out now that we have this recorded on tape and there will be proceedings of this made available. I'm glad that you mentioned this because we need to know, and the right people need to know about it. I was not aware of it because I have not seen any report as to what you had done, and where we are in our deliberations. When we go to our superiors we have to have a report or we don't have anything.

Dr. Beierwaltes:

The area where there is, to my knowledge, no information available, one which might very profitably be explored here (with suggestions made by this group, because I certainly have no answer to this at all) is a newer problem that we have found very important and pressing. We have no solution to the problem of the radiopharmacists.

In the olden days when we had only two radionuclides, ^{131}I and ^{32}P, it was very simple to know who your paramedical personnel were (besides some technician that you trained yourself); they were the radiation health physicists. The doctor injected the radionuclide into the patient, and the radiation health physicest took care of the problems of strictly radiological health. But starting years ago our hospital pharmacist came to me with his problem of the radiopharmacist; I said, "Well, I suppose we don't have any drugs. We have two radioactive isotopes and that's it." This has come back repeatedly.

During the past two years it occurred to us that things have changed radically since those days and what has brought it about is the rapid development of a wide range of new radionuclide labeled compounds. At first this didn't bother us because these were sold to us by pharmaceutical companies where the problem of pharmaceutical purity was very well managed so that we didn't have to worry about it even from a legal standpoint. But when we started to get our own generators and cyclotron-produced radionuclides, and reactor-produced radionuclides (which precipitated our biggest problem, the ^{18}F from our reactor) then we had to get together with the pharmacy and say, "Well, here's ^{18}F. It has a physical half-life of 109 minutes. What about bacteriologic purity, the pyrogen-testing, and so forth?"

Now the radiation health physicist talks to me almost daily about the necessity of a radiopharmacist. Now, theoretically, in a university setting, we can do anything we want to do. But the next question then is, "What constitutes a radiopharmacist, and what should his background be?" Well, we started out by having our radiation health physicist trained in the proper way by having him teach a course in the School of Pharmacy. We thought that would be the best way to get him educated. It was, but he was immediately bought off by a radiologist who was in private practice for $22,000 a year. So our tentative approach now is to take a girl who has a bachelor of science degree in chemistry and is registering for 4 hours of credit courses in the School of Public Health in their radiological health program. She has been a technician in clinical nuclear medicine for 2 years. We will have her continue to work with us and get her radiological health from a good type of background--she's got her chemistry--and have her teach in the School of Pharmacy. But we certainly would love to have a curriculum for the training of a radiopharmacist, and any suggestions that anyone here may have, I would like to hear.

Dr. Harper:

The University of Chicago has had the longest experience in this general area.

Dr. Maxfield:

I would like to say how much I believe that the need for improved training of technicians is really something that is countrywide. Dr. Kuhl is right in that training in a 4-year program won't help us immediately, but it certainly will upgrade our training program in nuclear medicine labs in the future.

In our own area, all of our technicians are on-the-job trained, and our senior technicians become senior technicians by longevity of employment, which usually is about 3 years. I feel there is also a very marked need of some way of giving the people, who are currently our chief technicians, some interim academic training in what they are actually doing in nuclear medicine. The majority of these people are very competent in setting up a scan and very competent in setting up and doing counting procedures. But if anything goes wrong with the instrumentation, or there's a little variation from the routine technique, they really have no knowledge of what is happening. This was brought home to us very effectively recently when our chief technician was away for a few days. The spectrometer on one of our scanners drifted slightly and the other three technicians in the laboratory threw up their hands and said it was completely out of working order and nothing could be done. Something very basic is needed to upgrade the level of training and level of knowledge of the technicians in nuclear medicine. I think this is something that needs to be done immediately. Possibly short courses could be held in different places across the country, or in some area like Oak Ridge. This is the way the physicians initially were trained (with initial courses that they could go to) before we really got into the field of training physicians, the way that it's done now in basic nuclear medicine.

Another point that was brought up by Dr. Beierwaltes concerning radiopharmacists is very definitely one that is needed. The problem you have, when you start trying to do your own tagging and setting up your own tagging of materials in the hospital is: Who is to help supervise the chemical purity and the pyrogenicity and testing for the materials that you're going to use? This is certainly something that is needed.

Dr. Harper:

Our solution to the pharmacist problem was merely to hire a pharmacist, and if we can find one with a chemical background so much the better. His training in radioisotopes consists of working along with us and our technicians, our chemist technicians and learning to develop compounds. When he gets to the point where he can be used, he handles the routine preparation.

We had an opportunity to see how this worked recently when our regular pharmacist went back to India for a 6 weeks vacation, and one of the boys from the other pharmacy had to come over and fill in. He had a minimal background, but he was able to function quite competently. There was some anxiety at first, but he was able to make preparations, tag albumin with technetium and put it in the mouse. He saw that it had the right distribution before giving it to the patient. He would assay it. This has worked out quite satisfactorily as far as we are concerned. It's an expensive solution--pharmacists don't come cheap.

Dr. Workman:

I think from what has just been mentioned about training technicians, it should be brought out that the Society of Nuclear Medicine is also trying to upgrade the training of our technicians at the chapter level. In the Mideast Chapter we have had some refresher courses in the last 3 months. Two were held in which we tried to upgrade the training of the technical affiliates--that's what they're called in this group--and I think there is an effort being made all over the country along the same lines. I don't know whether everybody is aware of this or not.

Dr. Saenger:

I just wanted to say one thing in answer to Dr. Kuhl. The 4-year program which is being developed is really to get a medical technologist who then could train a 2-year individual. He would be a chief technician as you proposed. I forgot to make that point.

Dr. Smith:

The approach that we have taken to try to solve the radiopharmacy problem is to get a pharmocologist who is obtaining his Ph.D. to join our group. We then let him train and supervise technicians to this end. Hopefully, he is able to produce technician-level radiopharmacists. They are then under the direct supervision of a registered pharmacist who also has his Ph.D. in pharmacology.

Dr. Brill:

We have been attempting to help in this area of technologists training by enticing physicists to our area. They get to know the problems of nuclear medicine and can apply their skills to the solutions of many of these problems. I really don't have either the ability or the time to teach technologists as well as they should be trained, and I think many of us have this problem. I think that to set up many technologist training programs we're going to be faced with staffing these programs with people who can actually communicate the kinds of information these people need to know, and can direct them toward some of the clinically relevant areas. I think going through standardized curriculums in physics, mathematics, and instrumentation would be far less relevant to them than if we can find people who have the specific training and experience in nuclear medicine, and who are trained in basic science, to conduct these technologists training programs. I think we really need people with advanced credentials to function in these technologist training programs, as well as the people to train. I think the first person to concentrate on has not yet been secured, the teacher.

Dr. Becker:

I think it is very important to emphasize the necessity for organized technician or technologist training. But I think it is also very important to support and encourage onsite training, the kind of thing that Dr. Maxfield has mentioned. Some of the rest of us have been involved with training these technicians when they get to our laboratories. It's well and good to have somebody trained in the basics elsewhere, but the problems we have encountered come when we take into our staff a well-trained technologist--who is well trained, but does things just a little bit differently. We all do things a little differently, and it's probably just as well--our techniques all vary slightly. But it's very hard sometimes to get these people to accept the fact that there are other ways of doing things than the ways they learned. This is a constant problem. We have actually reached the stage where we do not want technicians who were well-trained elsewhere. We would prefer to train them ourselves. This is difficult because we frankly do not have the facilities to train people as well as they might be trained elsewhere; on the other hand the problem of retraining somebody or making these people reorient themselves to our way of doing things is such a chore, and causes such a disturbance in the morale of the laboratory that we are discouraged by the prospect.

The other thing I would like to mention is that in a number of institutions around the country, the technicians, presumably well-trained technicians, run the laboratory. The physician is a part-time participant in the laboratory and the technician runs the laboratory. I know of five or six laboratories in our area that work this way. Then when a physician moves in and attempts to exert an influence, he meets the resistance of a well-trained technician who has been reading the reports and giving interpretations. I think we have to somehow fit this situation into our training program.

Dr. Maxfield:

In reply to Dr. Becker's comments about on-the-job training, the point I want to make is that these people become very technically proficient as knob-pushers and in following the set procedures. But when you start asking them a little bit about the instruments they are using or a little bit about the math of the calculations that they are doing, then I think this is where they fall down in their basic knowledge. I think that anyone who has basic information about how a unit works, and why it works, and what they're really doing, can learn the technique of the laboratory they are working in. I was not trying to stress the clinical side, because this does vary from laboratory to laboratory. My point concerned the basic understanding of the operation they really were doing. This is what is lacking in most technicians who are trained on the job. They come into a situation because they are picked up when there is a vacancy in the laboratory. They are taught how to do a procedure step-wise, such as to set up a scan. But nothing is learned about the function of the scanning unit, or how it actually works. So this is where, I think, we need additional training for the technologists. Someone who has this knowledge should be able to adapt very well to any laboratory.

You find the same sort of thing with X-ray technologists who have had 2 years of training. They go out to a radiologist's office, and since each radiologist wants to have his films taken a little differently in density--things like this--they know how to do it. Our problem is that most of our technologists in the field of nuclear medicine do not really have training equivalent to that of the average X-ray technologist. Sometimes you even wonder how much the X-ray technologists know about their field when you get into problems, and they don't really know how to vary the exposure of the films the way you think they should. We have run into this because two of our technologist in nuclear medicine are trained as X-ray technicians and do occasionally take films for us on localization of our isotope procedures. We have trouble having them get the correct density on the X-ray film, so that they are not even really good X-ray technologists.

Dr. Hilberg:

Before I dismiss you I would like to take this opportunity to introduce to you the moderator for this afternoon, Dr. Herman Slatis. He is Professor of Zoology here at Michigan State University and has been trained at the University of Chicago. His primary interest is the field of human genetics. He has had considerable experience at the Argonne National Laboratory of the AEC. He will be in this position this afternoon.

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SECOND GENERAL SESSION

INTERNAL RADIATION DOSIMETRY

Edward M. Smith, Sc.D.[1]

The topic for discussion at this point is the absorbed dose resulting from biologically distributed radiopharmaceuticals. My own interest in this field originated in graduate school, and I have had an active interest in this area since then.

The primary importance of calculating the absorbed dose is to have an estimate of the possible risk to the patient so that the benefit from a diagnostic procedure utilizing a radioactive material can be weighed against this risk. Secondly, an accurate estimate of the absorbed dose will enable the physician to utilize a maximum activity of the radionuclide (radiopharmaceutical) for a particular study, that in his professional judgment is required, to obtain the needed statistics; that is, detected photons, to clinically justify the procedure. The patient will be needlessly irradiated if a statistically significant study is not performed, irrespective of the radioactivity required (and the resulting radiation dose to the patient) since no useful diagnostic information will be obtained.

In the past 2 or 3 years the interest in this particular area of nuclear medicine has increased. This is most apparent by the fact that scientific journals are allowing more space for this data, whereas before this type of information was to a certain degree being deleted, and this deletion, justified by saying, "Well, it's of no real value; just put down the numbers and don't bother with the assumptions and all of the rest of the things that go into the calculations."

I would like to devote a major portion of my presentation to bring everyone up-to-date with the activities of the Medical Internal Radiation Dose Committee of The Society of Nuclear Medicine. This is a committee that was started in November of 1964, by the urging of John Hidalgo, Craig Harris, and representatives from two radiopharmaceutical manufacturers who had biological distribution data and did not know what to do with this information. Since then, this group has grown from the original six members of the committee who attended the first meeting in November of 1964, to an 18-member committee today. Four of the six original members of the committee are still active on the committee. To date, we have had approximately 10 meetings with 50 to 75 percent of the members attending each meeting.

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The committee is composed of individuals in various areas of nuclear medicine and one individual who had no previous interest in nuclear medicine before he became associated with the committee. The individual I am referring to is Dr. Martin Berger of The National Bureau of Standards, who has been applying his theoretical physics background to calculate complex physical parameters that are required for internal absorbed dose calculations. Among the most important of his contributions are the energy buildup factors for low energy photons, so that one can calculate point-to-point absorbed dose without having to assume a simple point kernel consisting of only inverse square loss and exponential attenuation. He has also been working on the calculations of absorbed fractions for beta spectra and monoenergetic electrons.

In October, 1965, the committee received a grant from the Division of Radiological Health, U.S. Public Health Service, now the National Center for Radiological Health. Currently we have a grant application pending for continuation of this support for 5 additional years.

The original objective of our committee was singular, and in fact still is. Quoting from the minutes of the committee's first meeting in November of 1964:

> "To provide the best possible estimate of the absorbed dose to patients, resulting from the diagnostic or therapeutic use of metabolically administered radiopharmaceuticals, with the restriction"(and I emphasize this) "that the Committee make no judgment as to the medical significance of the estimated absorbed dose."

Our aim is to provide the best estimate of the absorbed dose. The clinician must then use his own judgment.

To reach this primary objective, the committee has set out to do the following work:

(1) To collect biological data for a given pharmaceutical product. We are not particularly interested whether the pharmaceutical is tagged with ^{131}I, ^{125}I, or ^{130}I. We collect the biological data for the pharmaceutical product, and then we calculate the absorbed dose for any of the radionuclides it may be tagged with. In some cases it is advantageous to work with the longer-lived radionuclide, in other cases the shorter-lived; however, if one is to be able to calculate the absorbed dose for any of the radionuclides a pharmaceutical may be tagged with, the data must be available for both the initial interval of time and the long-term data. For example, short-term data (first 6 hours) is needed for ^{132}I, while long-term data (6 months or more) is needed for ^{125}I studies. These data are required because when a large administered activity of a short-lived radionuclide is utilized, an entirely different organ may receive the highest absorbed dose than when a smaller activity of a longer-lived radionuclide is

used. This effect can be magnified by the biological properties of the pharmaceutical being tagged; for example, if a pharmaceutical is very promptly excreted and only a small percentage is retained in the body for a long period of time, the bladder may receive the highest absorbed dose when a short-lived radionuclide is used, while for the longer-lived radionuclide the organ that concentrates this material may receive the highest absorbed dose.

(2) We decided that we must evaluate the best way to calculate the absorbed dose as we could no longer utilize the methods that were adequate 10 or 15 years ago. At this time, we only had to worry about ^{131}I and radium, thus the methods of calculating the absorbed dose were based on these radionuclides that emit relatively high energy photons. In addition, these earlier techniques introduced an artificial dichotomy between particulate and photon radiations which is completely unnecessary and in many cases results in both errors and confusion in the calculation of the absorbed dose. The problem of determining the optimum way of calculating the absorbed dose has been, to date, one of the primary fields in which the committee has been working. Finally, I think we have decided on the method of calculating the absorbed dose which is acceptable to all of the members of the committee.

(3) Another important aspect of the committee's work is to obtain accurate nuclear data. This may sound as though this data should be very easy to obtain, but in many cases it is very difficult to acquire especially for a few of the radionuclides now being used in nuclear medicine. For example, an accurate decay scheme for ^{123}I or ^{113m}In is not available, and the decay scheme for ^{197}Hg is being continually revised. These data are gradually becoming available for the radionuclides of interest in nuclear medicine, but in many cases considerable effort must be expended to obtain this very important data.

(4) Another important area involves the evaluation of the effects of radiochemical impurities, radionuclidic impurities, and variations in the physicochemical properties of the radiopharmaceuticals on the absorbed dose. A good example of this is the physical characteristics of macroaggregated albumin on the biological half-time of this material in the lung. One product may have a biological half-time in the lungs which is 4 times greater than that of another product. Obviously, this has a marked effect on the absorbed dose to the lung. These factors must be evaluated when absorbed dose estimates are made.

(5) The proper techniques of calibrating radionuclides in the nuclear medicine laboratory are being studied. This is especially important with the increasing use of short-lived radionuclides and radionuclide generators in the nuclear medicine laboratory.

(6) The method of expressing the absorbed dose that a patient receives is being considered so that the inherent uncertainty

of these calculations may be adequately portrayed to the individual utilizing this information. Ideally, the committee would like to develop a means of expressing an upper and lower estimate of the absorbed dose for various groups of individuals that would be studied by a given procedure. However this objective will not be fulfilled in the near future.

(7) The effects that age and pathological state of the patient have on the absorbed dose are being evaluated.

(8) Finally, and of utmost importance, is the actual calculation of the absorbed dose for a radiopharmaceutical and the presentation of this data in a usable format for the individuals in the nuclear medicine field.

The first group of pamphlets that the MIRD Committee will publish will appear as a Supplement to the Journal of Nuclear Medicine, in January 1968. This first Supplement will include the following pamphlets.

(1) "A History of the Medical Internal Radiation Dose Committee of The Society of Nuclear Medicine," by Edward M. Smith.

(2) MIRD Pamphlet No. 1 - "A Schema for Absorbed Dose Calculations for Biologically Distributed Radionuclides," by Robert Loevinger and Mones Berman.

(3) MIRD Pamphlet No. 2 - "Energy Deposition in Water by Photons from Point-Isotropic Sources," by Martin J. Berger.

(4) MIRD Pamphlet No. 3 - "Absorbed Fractions and Specific Absorbed Fractions for Photons," by G. L. Brownell, W. H. Ellett, and A. R. Reddy.

The second group of MIRD Pamphlets should be published in the summer of 1968 as Supplement No. 2 of the Journal of Nuclear Medicine. This supplement will include absorbed dose calculations for Neohydrin, selenomethionine and macroaggregated albumin. These will include the calculations for all of the radionuclides that these pharmaceutical products may be labeled with. In addition there will be tables of absorbed fractions for monoenergetic electrons and beta spectra. The other radiopharmaceuticals, which are under study and are approaching a sufficient degree of completeness with respect to the collection of biological data, are xenon gas, ^{99m}Tc in various chemical forms, ^{113m}In in various chemical forms, and the ionic form of iron, strontium, and calcium.

To facilitate the detailed calculations required to evaluate the absorbed dose to the various organs of the body, Dr. Mones Berman at the National Institutes of Health, who is a member of the committee, has developed a computer program for absorbed dose calculations. This program is essentially complete, and all that remains is to verify the computations of the program. The program will be on magnetic tape or punched cards and will be available to interested individuals. The program is set up in a modular format, so that kinetic data for various radiopharmaceuticals can be entered as well as the various parameters needed for the computations. This program also includes the capability of evaluating the error associated with the absorbed dose calculation as well as providing the estimate for the absorbed dose range.

The MIRD Committee is actively working or cooperating with various national and international organizations, which have an interest in the field of internal absorbed dose. These agencies include the International Commission on Radiological Units, the International Atomic Energy Agency, the National Center for Radiological Health, the U.S. Atomic Energy Commission, and the Food and Drug Administration. The relationship with the latter organization will be a close one since we are trying to develop a master file of biological data and absorbed dose calculations. This master file will be available to manufacturers of radiopharmaceuticals who wish to utilize this data to prepare their package inserts. At the last meeting of the MIRD Committee in Seattle, representatives of the radiopharmaceutical industry were invited to attend the committee meeting as observers.

The most important activity of the MIRD Committee in the future will be to stimulate the collection of biological distribution data for radiopharmaceuticals. It is hoped that when new radiopharmaceuticals are developed, the necessary biological data to calculate the absorbed dose will be obtained while the radiopharmaceutical is being evaluated. A significant amount of work lies ahead in the area of developing biophysical models for calculating the absorbed dose to specific organ systems; for example, how do you calculate the absorbed dose to blood? This is rather a straightforward question, but one that is very difficult to answer in a precise manner. This same question applies to the calculation of the absorbed dose to both bone and bone marrow, with the added difficulty of defining the tissue for which the calculation should be made. This brings one to the point of calculating the absorbed dose at the suborgan or cellular level. This consideration is becoming more important with the increasing use of ^{14}C and ^{3}H for in vivo studies. In addition, a greater effort will have to be spent in developing rapid and reliable methods to evaluate radiochemical purity and assay methods in the clinical nuclear medicine laboratory.

The above considerations indicate the importance of absorbed dose calculation in nuclear medicine.

DISCUSSION

Dr. Slatis:

We are open to discussion now.

Dr. Smith:

May I open the discussion?

Dr. Slatis:

Yes. I thought I saw someone's hand up before yours, but you may start.

Dr. Smith:

About 3 weeks ago, I distributed to approximately 60 medical centers throughout the country a questionnaire based on the experiences we have had in our laboratory with ^{99m}Tc sulfur colloid over a 3-month period. The following is the text of the questionnaire:

"Dear Doctor:

> We have experienced one serious and two minor allergic reactions, which may be closely associated with the intravenous injection of ^{99m}Tc sulfur colloid, prepared by the thiosulfate-dextran method in our laboratory. Since there is a long delay in the dissemination of this information by the usual means, I am relating our experience in this manner. We would appreciate knowing if you have had any similar experiences. Please check the appropriate blocks below and return the questionnaire in the enclosed self-addressed stamped envelope. The results of this survey will be forwarded to you."

The members of the audience who have received a copy of this questionnaire and have returned it, will find a copy of the results of this survey in their mail when they return to their laboratories. To briefly summarize the results of this survey, we found that there were about 8 methods of producing ^{99m}Tc sulfur colloid. One can infer from the results of this survey that there were no significant reactions to ^{99m}Tc sulfur colloid unless dextran was employed in the manufacture of the material. Of the 10 institutions that prepared the colloid with dextran, 6 of these institutions reported at least one "anaphylactic reaction" or "anaphylactoid reaction." This amounted to 11 reactions in approximately 1,300 studies performed. In over 3,000 procedures performed with the colloid prepared with gelatin, there were only 3 minimal reactions, and these could not be directly associated with the sulfur colloid. The results of this survey will be submitted to the Journal of Nuclear Medicine as a Letter to the Editor. (See Appendix for the survey results.)

Dr. McCormack:

I would like to make a comment on the reactions as described in your report. This problem with new radiopharmaceuticals--I think maybe this is a little off track, but when one has a reaction to a radiopharmaceutical within his own laboratory I think what you do is try to trace this down specifically and statistically. This looks very much like it would incriminate dextran, and I think this is very real because the reactions of this type are quite typical. We have skin tested one patient who had an anaphylactic reaction and did not find any reaction to dextran epidermally after 6 months. Again, this isn't unusual, but I hope we can keep this in mind. When you have these patients, try to keep track of them, not only with this pharmaceutical but with others so we can pinpoint these things as specifically as possible. But this looks like dextran.

Dr. Numerof:

Will a skin test indicate whether a patient will be sensitive to dextran?

A Voice:

No, it's not a sine qua non at all, but it's of the allergy-type testing that is available. The intradermal testing is probably the most sensitive, but it isn't foolproof.

Most people, after an anaphylactic reaction, are anergic, because of using up all of their response; also, an anaphylactic reaction implies that the patient has previously been sensitized to one of the agents in the injection.

Dr. Harper:

We keep hearing a great deal about pyrogens and pyrogenic reactions, and we all know about the difficulty and expense of dealing with rabbits. I was wondering if you had collected any data on pyrogenic reactions; or just ball park-wise, how many people in the audience have really seen a pyrogenic reaction from one of these preparations?

Dr. Smith:

There was one case reported when carboxymethylcellulose was used in the preparation of the colloid, and this was attributed most definitely to an old solution. This material was only used 5 times in humans and was stopped.

Mr. Harris:

One of the worthy things this committee has been doing, to which Dr. Smith alluded, is to put competent nuclear data into the hands of the nuclear medical practitioner. For many years all we could use was the old edition of Slack and Way's Radiation from Radioactive Atoms, and one of the least tangential efforts of the committee has been to try to secure the preparation of a second edition. I could ask you this privately, Dr. Smith, but it might be well to ask it in front of the others. "What is the status of your last communication with Dr. Katherine Way of ORNL toward the second edition of Slack and Way, that is to come out in the B Section of Nuclear Data?"

Dr. Smith:

I have not spoken with Dr. Way for quite a while, but the last communication was just before the meeting we had at Cedars in Miami, when I received the latest decay scheme data from her. I haven't heard from her since then, so I don't really have any idea whatsoever.

Dr. Snyder:

We work in the field of occupational exposure more, but of course many of these dosimetric problems are the same. So a year or so ago we secured the services (the summer services) of a professor of physics who specialized in the field of decay schemes. We now have an operating code which takes the information in almost any available form--it doesn't have to be quite specific--from a decay scheme and it will give you a printout of the main list, including the auger electrons, the internal conversion of electrons, gamma rays, X rays, and so on. This will be published in our annual report. I have about 10 copies of the paper with me for those of you who would be interested in the gory details of it. It also gives you the average energy of each of the beta rays that it puts out, taking into account whether it is first-forbidden or second-forbidden or what-not kind of spectrum that you have.

I have also available perhaps eight or 10 different isotopes that we worked out as examples to bring to this meeting. These codes are rather new, so we have not at this point built up a tremendous library on different isotopes. We plan to extend this, of course, and would be glad to make them available to you as we have them.

I might mention too, that we also have been calculating absorbed fractions; and sometime--perhaps during this symposium--I can tell you a little more about that.

Dr. Smith:

I should mention something in comment to Dr. Snyder's comment. The factors that are in our pamphlets have been verified by Dr. Snyder's group, and they agree within better than 1 percent in most cases. They have been agreed to by--his Monte Carlo method is a little bit different than the method used up at Mass. General--Gordon Brownell's group, and Martin Berger has verified these by using the moments method, so there's absolutely no question that these numbers are valid and reliable, because they've been approached from three entirely different physical techniques with three entirely different physical configurations. The only question which we throw back and forth now at each other is: Are we talking about bound media or are we talking about unbound media, and if it is water, can you extrapolate from water to striated muscle, and so on. This is sort of getting down to miniscules, which we may be pushing a little bit hard.

I would also like, if possible, for our committee to see this code. We could probably utilize it in our publication so it will be consistent with other people's notations.

PRODUCTION AND USE OF SHORT-LIVED ISOTOPES

Paul V. Harper, M.D.[1]

I thought it might be appropriate, in view of the fact that most of the sweeping generalities about short-lived isotopes have already been made principally by our keynote speaker, to look at the questions such as: Why do we want to use short-lived isotopes, and how do we tell whether we are doing any good using them?

Henry Wagner has a nice presentation in which he shows that if you are looking at a physiologic process that takes, say, an hour, that the ideal isotope to use from the point of view of information retrieved for a given radiation dose to the patient has an average life of about an hour, which seems very reasonable. A beautiful example of this is using ^{15}O to look at the exchange of oxygen between molecular oxygen associated with the hemoglobin, and the oxygen in the water of the blood. This exchange takes place very rapidly, being complete in a few minutes. The half-life of ^{15}O is 2 minutes, which matches the duration of the physiological process almost perfectly. The problem is that it doesn't work out quite this way in real life in very many cases, and there are some very violent deviations from this principle that the physiologic process and the average life of the isotope should be of the same order of magnitude. For instance, in doing kidney scans with ^{99m}Tc, the best pictures are obtained at 24 hours, 4 half-lives later. At the other end of the spectrum with ^{75}Se in the pancreas or the parathyroid, the agent has a 100-day biological half-life and 127-day physical half-life, to look at the process lasting 30 to 60 minutes. In either condition, one still gets what we like to call acceptable radiation dosage to the patient. Thus there are other parameters besides the physical half-life of the isotope that may be strongly controlling in a particular clinical situation.

My first exposure to this problem was many years ago when I discovered to my horror, that a thyroid scan with ^{131}I cost the patient approximately 100 rads to the thyroid gland. This was about when we discovered that radiation to the thyroid apparently produced carcinoma of the thyroid in children. Thus thyroid scanning seemed like a rather frightening thing to do to somebody, even to an adult, especially in view of the rather limited information we usually get from thyroid scans. This unpleasant situation has survived for many years without much alternative.

Let us look at the chart of nuclides. These may be regarded as acts of God. There isn't much you can do about them except to try to choose one appropriately to fit a particular set of circumstances. Looking at a table like this, you are obstructed by the phenomenon that things either are thinkable or unthinkable. We were, of course, looking for something that would cause less radiation dosage to the thyroid gland, and who would ever think at first glance that an isotope with a half-life several times as long as ^{131}I might be preferable. By some combination of circumstances we happened to look again at ^{125}I. This was at the same time Bill Myers was doing the same thing, but fortunately we didn't know about it, so we were able to proceed independently. Looking at ^{125}I for thyroid scanning, with the idea of reducing radiation dose, is very instructive and involves many of the parameters that one has to consider in this whole problem so that it is not as irrelevant as it might seem to the question of using short-lived isotopes, even though paradoxically it is long-lived.

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The sort of things to be considered in making a comparison are: using classical dosimetry, depending somewhat on what biological parameters are used, one gets approximately twice as much radiation dose from ^{131}I as from ^{125}I, microcurie for microcurie; considering available photons per disintegration, one gets approximately twice as many photons per disintegration from ^{125}I as for ^{131}I. The main problem with ^{125}I is that the radiation energy is so low that much of it is absorbed in the thyroid and overlying tissue so that one loses a factor of about 2 here. The collimator can be made about twice as efficient for ^{125}I. In the sodium iodide crystal you count all the photons with ^{125}I, but have only about a 50 percent photopeak efficiency for ^{131}I, so you gain another factor of 2. A crystal with a beryllium window instead of the usual aluminum container gives almost another factor of 2 in efficiency, and since the ^{125}I radiations are almost completely absorbed and detected in a 1/8-inch-thick crystal, the background can be reduced by a very large factor compared to ^{131}I.

Further than this, we were consulted by Bill Schindler, a physiologist at Baylor, who had been trying to observe the effects of ^{125}I in mice. He found that when he gave 200 microcuries of ^{125}I to a mouse, 20 to 30 percent went to the thyroid with an effective half-time of 3 or 4 days. When the radiation dose to the mouse's thyroid is computed it comes out to be of the order of a hundred thousand rads. However, the mice survived and months later their thyroids were almost normal histologically, whereas similar doses of ^{131}I destroyed them completely in a few days. Apparently the explanation for this phenomenon is the fact that almost all the iodine in the thyroid gland is in the colloid, and most of the radiation dosage to the mouse thyroid is due to the low-energy Auger electrons and soft fluorescent photons, so the thyroid is self-shielded from the radiations of ^{125}I for all practical purposes. In the current 1967 Handbook of Nuclear Medicine there is a beautiful picture of this phenomenon going on in a radioautograph of the thyroid with ^{125}I showing all the tracks in the region of the colloid where there are no cells, and where radiation dosage can do no harm. When you scale this up to a human thyroid, you only gain about a factor of 4, as there is a significant absorption of the 27 to 35 keV photons, and if you're going to be practical and use available equipment, a ^{131}I collimator, an ordinary crystal with a thick aluminum can, you lose a factor of 4 again, but still there's a rather impressive gain for ^{125}I. One of the most impressive things about it, to me, is the microdosimetry which Ed Smith alluded to briefly.

Another situation where microdosimetry may be relevant is in the kidney where the isotope is distributed in the cortex in a very irregular manner, and perhaps half the cortex is spared from the locally absorbed radiation, the beta dose. The distribution of mercurials in the kidney cortex and of technetium-iron complex --while it may not be identical microscopically--grossly looks about the same, so that it's possible that the dose calculations, assuming uniform distribution in the cortex for the beta component of the radiation dose, ought to be increased by a factor of 2 or so in this particular situation. In view of the fact that radiologists start worrying about kidney function, especially in hypertensives, when the dose gets up around 100 rads or so, this causes substantial worry about ^{203}Hg for brain scanning.

Let us get on to short-lived isotopes. There are a number of these that are available from reactors, from generators, and from accelerators, and of course the generators themselves come from reactors or accelerators. Some of the short-lived isotopes can be made in a variety of ways, like ^{18}F, which is potentially one of the most useful. Even though it has only a 2-hour half-life, people were remarking at the Seattle Nuclear Medicine Meeting, that if one lived within a thousand miles of a reactor it was feasible to consider using ^{18}F. Separated 6-hour ^{99m}Tc is currently being shipped across the country for clinical use. While transportation problems don't exist nearly so much with generator-produced isotopes, there remain some problems with these. With ^{99m}Tc, the parent is short-lived so that you have to keep buying it, and it gets pretty expensive. For a substantial operation, the cost can be of the order of $30,000 to $50,000 a year. If you use a long-lived parent such as those for ^{113m}In or ^{68}Ga, you solve this problem to some extent, but then you run into problems of bacterial contamination. A short-lived generator which becomes contaminated poses no problem, but a large long-lived generator represents a substantial investment.

Indium 113m (^{113m}In), ^{68}Ga, and ^{99m}Tc can be regarded as general purpose isotopes in the sense that they can be manipulated very readily to form numbers of different compounds. Technetium 99m (^{99m}Tc) in various forms may be used to visualize the thyroid, brain, subarachnoid space, the lung (by perfusion or inhalation), various blood pools, the liver, spleen, bone marrow, and kidneys. The same can be said with ^{113m}In and ^{68}Ga (with the exception of the thyroid, of course), and probably with ^{123}I. These are all materials that have to be considered seriously in terms of which one is preferable. Bill Myers has been talking about the number of usable photons per unit radiation dosage to the patient for a number of years and Ed Smith has been talking about how to compute the unit radiation dosage. How to decide what is a useful photon is not quite as simple.

The statistical figure of merit, proposed by Dewey and Sinclair and Bob Beck and used by Christine Matthews and a number of others, I believe to be the best available criterian for this purpose. The mathematical models of perception, which have been worked out by Rose, Russell Morgan, and Coltman, in mathematical terms are formally identical to the formulation that is used for the statistical figure of merit, the only difference being a normalizing factor. So the figure of merit, which ostensibly gives a statistical probability for detection, probably also is a meaningful criterion for perceptibility.

We have recently done a preliminary study on figures of merit for ^{99m}Tc, ^{68}Ga, and ^{113m}In in a variety of situations, which Katherine Lathrop presented at the Nuclear Medicine Meeting. These figures of merit are in a sense inverse detection times. The larger the number, the shorter the time it takes to detect the difference between the target and nontarget regions. The target regions are defined as 1-inch lesions in everything but the lung where there are 2-inch lesions. In the brain of course the lesion is hot, while in the kidney, liver, and lung it is cold. Lesions are placed at different positions in the liver and the lung. Measurements were made both with the Anger camera with the appropriate collimation, and with the 3-inch magnascanner, with what we thought was the appropriate collimation, as these were the devices available to us. The values obtained are shown in table 1. Clearly the numbers are much higher with ^{99m}Tc. With ^{68}Ga, particularly with the scanner, they are quite low. In the lung they are, in some cases, exceedingly high. Of course in this situation we are integrating counts over a larger target region. The rather high value for the kidney with ^{68}Ga and the positron configuration of the camera are interesting. The situation with the positron detector of course is that it is count-rate limited to something of the order of 10,000 counts per minute. If one is looking at a large hot organ, the camera is flooded and it is not possible to give enough isotope to come up to the arbitrary level of 1 rad to the target organ. In the kidney with the 1-rad dose, the count rate first reaches 10,000 per minute so that the superior resolution in depth of the positron configuration is fully usable.

The somewhat lower values for the scanner, with the higher energy isotopes, using the 19-hole wide focus Picker collimator, are due to septal penetration. Using the 19-hole collimator, the line spread function (fig. 1) using ^{99m}Tc has a very narrow, high peak. Using ^{113m}In, the peak is substantially widened, and using the higher energy radiation from ^{68}Ga, it is spread out much more. So in using these different radiations, it requires a closer look at the type of instrument we use in order to decide which is preferable. If we had used a more appropriate instrument than this, the comparison would have come out differently. A 5-inch crystal with a thicker collimator would have had less penetration without sacrifice of efficiency.

Table 1. Normalized Figures of Merit

(1 rad to target organ)

Organ	Location of Lesion	Diameter of Lesion	^{68}Ga		^{113m}In		^{99m}Tc	
			Camera	Scanner	Camera	Scanner	Camera	Scanner
Brain	Center of head	1 inch hot 5:1	8.3	0.12	4.8	1.3	20.0	1.7
Kidney	Front to back	1 inch cold	190.0	2.86	15.2	3.9	87.9	7.0
Liver	Surface of liver	1 inch cold	5.3	2.50	51.9	8.9	191.0	39.0
	1 inch below surface		5.3	0.58	17.1	3.6	172.0	14.6
	3 inches below surface		5.3	0.13	8.2	1.6	41.7	2.9
Lung	Surface of lung	2 inches cold	25.5	78.00	507.0	75.5	5056.0	316.0
	3 inches below surface		25.5	37.50	217.0	32.4	2584.0	173.0

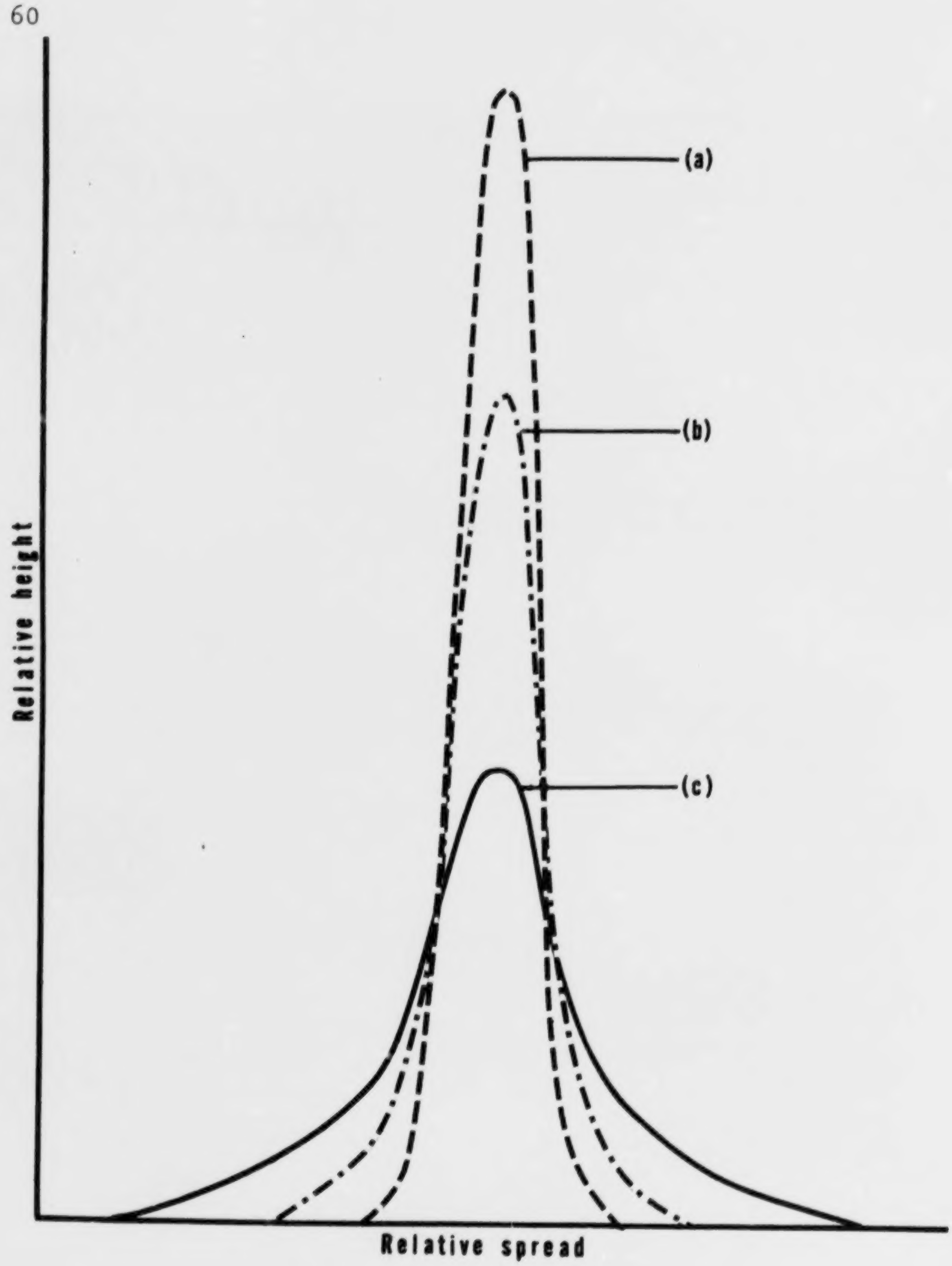

Figure 1. Resolution of a 19-hole collimator for (a) ^{99m}Tc, (b) ^{113m}In, and (c) ^{68}Ga

Determining these figures of merit was not a trivial effort. It is necessary to measure the count rates in the patient who has been given a known dose, and to normalize these to 1 rad to the target organ. The dosimetry and dose distribution studies must be done in order to arrive at this number. The object contrast is best determined for a comparative study in a phantom--this includes the effects of scatter. The collimator MTF is measured, using the line spread technique with the appropriate isotope and includes the effects of penetration. Data processing beyond pulse height analysis is not included in these figures. We thus require a large number of weighty factors to consider how to make a decision as to which one of these short-lived isotopes is best in a given situation.

It seems to be clear that in order to arrive at an optimal figure for a scanning situation (and these are the situation where the radiation dosage is much higher than any of the other situations in nuclear medicine) you really have to specify what you want to look at and what kind of count rate you are going to have in order to make an optimal choice in your system, and it would seem to imply that what you need for nuclear medicine equipment is flexible equipment, rather than a single device, and you must develop the judgment to use it appropriately. The situation is not going to be made any simpler by the medical cyclotrons that are coming into existence with ^{11}C, ^{13}N, ^{30}P with a 2-minute half-life, ^{18}F (more readily available), and a host of other agents. These, while they will not replace existing agents and methods, should allow one to look considerably farther.

Short-lived (20 minutes) ^{11}C sounds very favorable. However if you compute the radiation dose to the liver from this agent prepared as a colloid, it comes out to be just about the same as for ^{99m}Tc, even though the half-lives differ by a very large factor. So it does not seem, in this particular situation, where you have primary particle radiation to deal with, that some of these short-lived isotopes will be very helpful in reducing radiation dosage.

An interesting application of very short-lived isotopes has been developed at the Donner Laboratory by Anger and Yano, where they used daughter activities, of a few seconds in half-life which could be milked directly from a generator into the patient, thus illuminating the blood vessels going into the heart and out into the lungs. When the examination is completed, the radiation is simply turned off leaving no residual activity at all. There was a nice exhibit of this at the Seattle meeting. This has a favorable aspect in that one doesn't have to work with high activity because one is looking at a steady state situation. It can be scanned at leisure.

The short half-lived isotopes that I have just discussed don't seem to be reducing the dose to the patient very much, but within the prescribed conventional limits of what is acceptable dosage to the patient, they are being used to obtain more information from an examination or to obtain the examination in a shorter time. For example, in our laboratory we do six views of the liver in less than one-half of an hour. We have the patient hold his breath during a single liver examination so that the respiratory movement doesn't blur the picture. I'm a little bit puzzled as to why the various committees, which we keep hearing from, always seem to dodge the question of how much radiation dosage it is justifiable to give a patient in a given examination. Perhaps some answer to this will come out in the present meeting.

DISCUSSION

Dr. Kuhl:

I think Dr. Harper points up a very interesting feature to which, perhaps, our attention shouldn't be directed: How to reduce the radiation exposure to the patient in nuclear medicine. Perhaps we really should direct our attention to improving the effectiveness of each rad of radiation that we use. Really we are mostly concerned about getting more information out of our diagnostic studies. We are not primarily interested in reducing the radiation exposure of the patients.

Dr. Becker:

Dr. Harper might be able to improve some of the already very good statistics for the ^{99m}Tc by using either the Oak Ridge design or the Brookhaven design of low-energy collimators, one of which is now available. These would give, perhaps, a factor of 2 or 4 in counting rate for the same rad, and therefore either allow the reduction in the dose to get the same counting rate he is achieving with the present collimator or to improve his figure of merit slightly.

Dr. Harper:

We don't quite feel that way, but maybe we're wrong. If you have a large crystal in a big shield and you want to use it effectively, you put on a narrow collimator with thousands of holes and you get a particular field of view reaching out into your patient. You can achieve the same field of view with a much smaller collimator and a 1/4-inch crystal and a detector that you can hold in one hand--1/4-inch lead shielding. This is what we actually have. I think the efficiencies are probably the same for this configuration as they are for the other configuration. If you want a big machine that you can use effectively with interchangeable collimators, this is obviously the thing to get. If you want a small device--I think this is similar to the one that you've been working with, Dr. Becker--where you can get multiple views with very light instrumentation, using low-energy radiation, you can do just about the same thing. This is one of the advantages of the energy that we're using in ^{99m}Tc.

Dr. Saenger:

I'd like to ask Dr. Harper about that cryptic remark about dosage with which he finished. What do you think is an acceptable dose to put into a patient?

Dr. Harper:

In our study we picked a rad to the target organ. Obviously, a rad to the liver doesn't have the same significance as a rad to the bone marrow.

Dr. Saenger:

Do you feel that age has any relevance in this discussion?

Dr. Harper:

Yes, and so does advanced malignant disease.

Dr. Saenger:

If you have these people above 40 years of age, who aren't genetically interesting, you don't have to worry about them, for example.

Dr. Harper:

I'm worried more about leukemia than genetic problems, at least at my age. I don't know. Do you have any feelings on this question?

Dr. Saenger:

Well, I'd like to find out what your feelings are. I'm not sure what mine are.

Dr. Harper:

You've been in this field for many years.

Dr. Saenger:

Well, my feeling is that I think you could talk about doses of perhaps 5 or 10 rads in older people if you have a situation which requires investigation. As I tried to point out this morning, I'm not so sure about how an individual is able to evaluate the benefits versus risks in terms of radiation risk, which in radionuclides seem to me to be rather minimal. I think when you're talking about acute high dose or high dose rate radiation, this is an area in which we at least have some practical epidemiological data to work with. For example, going back to studies such as the glands and radiation in pregnancy and things of this sort--when you start applying those doses and dose rates to nuclear medicine I don't think they are really very significant.

Dr. Myers:

With regard to comparing ^{125}I and ^{131}I, there's an additional factor so far as the biological half-time in the thyroid is concerned; it is very long. Then we get into the problem of what we mean, or what is the significance of the rad as a concept here. We have to get into the concept of the rem, because here the difference in half-time is a factor of 7 1/2 between these two nuclides. Now looking at it the other way, Dr. Harper, I've been thinking about this quite a bit and I don't know what the answer to it is. I'm thinking in terms of ^{121}I with the 2.1-hour half-life and ^{122}I with the 3 1/2-minute half-life. I can see some considerable potential in these isotopes when we get these medical cyclotrons around in all the hospitals. This brings up an issue about ^{11}C, ^{15}O, and so on; whether the rad may, or may not, rapidly become somewhat obsolete as a guide to us. Then we're really going to have to begin thinking in terms of rems.

INSTRUMENTATION

Edward M. Smith, Sc.D.[1]
Hal O. Anger, Ph.D.[2]
C. Craig Harris, M.S.[3]
Thomas G. Mitchell, Ph.D.[4]

Dr. Slatis:

An emergency arose and Dr. Ter-Pogossian could not attend. In his place we have arranged for a panel type discussion.

I, personally, had been against this, thinking that there weren't any problems of instrumentation; it's obvious that we do, since some have been brought up already. I think the proper way to start is to ask Dr. Goodrich why he got up and asked about instrumentation this morning, and if he would like to begin this discussion. This is the privilege you get for having opened your mouth.

Dr. Goodrich:

It's kind of like going into a candy store and then deciding which one of the jugs to start drawing from. We train our technicians, and we have some funds and some adequate equipment to make our clinical job a little easier, and we train our technicians in their use. Unfortunately, all laboratories don't buy the same equipment, so it is very difficult to train technicians on an instrument that has dials and indicators just 180 degrees different from those on another equally good instrument.

In scanning, this is true to a great extent because different companies have instruments that produce images that may look vaguely alike, but the information is recorded in all sorts of different ways. So it's impossible for one training center to teach technicians, and make them capable of going anywhere in the country to work with a wide range of different instruments, and not have them subject to criticism, such as, "This girl doesn't know anything about scanning." This is one aspect of the problem.

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The other is the instrumentation that is put out for your use, subject to instruction by the salesman who has read a brochure written by some college student who is working for the company during the summer. He has tried to make it simple and has drawn the wiring diagrams; this only makes it difficult. I have an expert working with me and there are times when he can't fathom it, so this is a direct criticism of the instrument companies. They should at least give us instructions that make some sense and tell the truth about the machine.

Mr. Simmons:

I would like to address my remarks to the first question that Dr. Goodrich raised about a technician learning to scan on one instrument and then going someplace else where they don't have that same instrument and then he can't do scans. This is the reason that we, in our training program, advocate a good basic science background for the people who are learning to be nuclear medicine technicians. We feel, instead of teaching them how to turn knobs on one instrument, you should teach them what each component of the instrument does, what the detector assembly does, what the amplifier does, what the pulse height analyzer does, how it does it, and so forth. Then no matter what type of rectilinear scanner they are using, they can take the instrument manual, even if they've never used this machine before, and within a short period of time they can get good scans with it. Similarly, in the case of imaging devices, I believe it might be a little bit more difficult to make the transition from one to the other.

We take exception to certain things that instrument manufacturers do, such as labeling controls on an instrument with some kind of exotic nomenclature that really has nothing to do with the function of that particular control. For instance, instead of labeling the switch "isotope range," why not call it "amplifier gain," which it is. So if we could have this kind of standardization from one instrument to another, it would be less difficult for a person to make a transition from instrument to instrument, providing he knew the basic functions of the components in the instrument to start with.

Dr. Goodrich:

I would like to disagree just a little. Certainly we teach, and I guess everyone does, the basic principles of the modules that go into a scanner, but they do not, in their photorecording, all operate on the same principle. One machine, for example, does not send any of its data through a rate meter for recording, whereas another one does. The gray scale on one instrument is a more digital presentation and it depends on its gray scale by the number of times it hits the same spot, whereas another one employs some witchcraft of voltage on the cathode ray tube to do this. Luckily it comes out with a pretty linear presentation, so it doesn't all happen just because there's a spectrometer and a rate meter hooked in line with the photorecorder.

Dr. Wellman:

I would like to add a point that good electrical engineering doesn't necessarily substitute for good mechanical engineering. Just because something works electronically doesn't mean it's designed well mechanically. Some of these electronic instruments are brought into the laboratory, but you can hardly get a patient near them, you know. There has been a real lack of good mechanical engineering, as well as the ancillary equipment to go along with the scanner, so that these things function as instruments to work with people. I mean, when a detector and a collimator arm just fall off an instrument now and then (as has happened in our laboratory) and just miss hitting the patient, it makes you sweat a little. This is something that needs some attention.

Dr. Harper:

I think it is ridiculous to think that a technician can come out of a technician's school and be an expert with all the different instruments. I mean, you come out of medical school and you have an internship. You learn how to fly if you're a pilot, but if you're a commercial pilot, you get checked out in the new type of plane before you run it. I agree that if you have a basic understanding of what the scanner is trying to do, it shouldn't take more than a day to get acquainted with an instrument so you can make reasonable scans if your supervisor knows how the machine works.

Mr. Harris:

I was trying to get my hand up a while ago, but I'm glad the discussion went on a little bit.

I think Guy Simmons' point--the words he said were right to the point. This takes me back, Bill Myers, to a conversation or a public discussion that you and P. R. Bell and I had in Oak Ridge in June of 1954, the one that got our little group into the act. One thing was very clear to us then, after about 6 years of working in the field of nuclear physics experimentation. We had to make our own instruments because we couldn't buy them. Because we used them for the purpose for which they were designed, we made pretty good instruments. At the time of the spallation of that group in 1956, I think we had some pretty good equipment. We learned from that a principle, and the principle is this (according to Percer Raymond Bell, and from anybody else it would still be equally valid): "Thou shalt not separate the function of the design of the instrument from that of its ultimate use." In this regard the instrument companies have let us down sadly.

That leads to such things as a labeling called "isotope range." The companies claim to be doing human engineering, but it's from where they view it--on their side of the so-called "ivory tower."

I was accused for many years of living in the "ivory tower" of Oak Ridge. Yet when I went to Duke in a clinical setting, I found I'm a lot more clinically oriented than that. Now the instrument companies simply do not use--whether they seek it or not I really do not know--the feedback from the clinical practice of nuclear medicine, because before they ever let the clinician see their instrument their engineering process is frozen, and they will not let you see it until their mind is already made up. Why is that? You are the reason; because all these years you have said, "Give me the cheapest thing that will do the job." You have robbed these people of the money they need to do the R and D, the time they need, and the money it takes to send a man out into the field to let him fool around out there a week without worrying about what he won't sell because he's off the road. You're going for the cheapest thing, and you've brought this on yourselves.

Dr. Ter-Pogossian's topic was to have been "The Next Decade in Nuclear Instrumentation." I would like to think that the next decade, if it does nothing else, would break us out of this vicious circle that is epitomized by a scanning instrument, produced by an instrument company, according to its own ideas of clinical use in nuclear medicine, and turned out to be an unconventional spectrometer. I wrote to them and I upbraided them about this. I said, "I think this thing is going to be hard to use, especially by those people to whom we have taught the generic type of spectrometer approach." "Oh, but you're mistaken. You're not in clinical medicine and you don't know what you're talking about." But I go and I talk to the owners of that machine and they say, "Oh, this would be a great machine if we had a conventional spectrometer on it." So this is a problem. Now what are we going to do about it in the next decade?

Dr. Maxfield:

I would like to amplify what Craig Harris said. I think one of the basic problems is that we still try to develop one unit to do all nuclear medicine, and I think all you have to do is look at any diagnostic X-ray unit and find that you have your X-ray tube that's set up to take chest films, you have a head unit, you have rapid-changers for blood flow studies, and you have a variety of units including a fluoroscopic unit for doing function studies on the GI tract. I think it's time that nuclear medicine grew up and recognized the fact that not one scanner is going to do everything equally well, and to start designing instruments to do one job particularly well, the way that it has been done in the field of diagnostic radiology.

Mr. Hidalgo:

I'm in the position of disagreeing with my colleague a little bit. Part of our problem has been, in the development of specialization, of trying to push toward a semiautomated or at least an assumed approach toward exotica in terms of automation of these machines with fewer knobs to twirl and fewer buttons to push.

I've had the questionable pleasure at times of going around to some of the elaborate exhibits at some of our national meetings--which are beautiful exhibits to me--and I walk around with some of our technologists who visit there, and we start going over a new scanning device or something like that and ask the question, "Where is the spectrometer?" We've got to find the engineer to show us, because it's usually hidden somewhere under some knob. Well, since I'm in the midst of the automobile manufacturing areas, I could make a parallel here with the disappearance of meters off the dashboard and the substituting of blinking lights. The blinking lights are very attractive, but the problem is that you really don't know what's going on.

If we're going to accept instrumentation that we can handle the same way as we handle an automobile effectively, this is fine, but we're not quite at that stage of development, and what we have to do from here on I think is to work toward systems.

I would have to say something nice about the instrument people because I think in most cases they have made serious, honest efforts--occasionally with mistakes--toward developing systems and working toward the end result as well. Some of their results have been happy and some of them have been rather disastrous. But I think I have to agree now with Bill that we have to go toward specific types of instruments, and these instruments have to be keyed, not only into the instrumentation but also into the system of measurement, the types of measurements that have to be made with patient convenience or the convenience of getting the patient under the unit, and so on. I think a lot of the things that we're doing, with exotic and unusual labeling of knobs, is causing us a great deal of trouble.

Dr. Maxfield:

I want to amplify one point. I did not intend to indicate that this should be simplified instrumentation, and it should be fully operational with all the dials and gadgets on it, but there is a need I think for selecting and designing instruments to do specific things.

Dr. Numerof:

The experience at the New York Chapter of the Society of Nuclear Medicine in this regard might be helpful to you. Within the past year we had a session called "The Ideal Nuclear Instrument," and we had a panel representing all of the major nuclear instrument manufacturers (one of them declined the invitation). We had different members of our chapter present his (and in one instance her) conception of the ideal clinical nuclear medicine instrument from the point of view of the physician, the physicist, and the technician. This was a rather instructive session, especially when one of our chapter members, who is a physician, was absolutely incensed when he said all he wanted in a particular piece of equipment was to have one other potentiometer put in to give him a little finer adjustment. He priced the potentiometer and it cost something like \$5.70, but the nuclear instrument person whom he had approached told him that the price would be something like \$1,200 to put a \$5.70 potentiometer in the unit. There was a lot of support for this individual case, and some of the economics involved, until one of the men from one of nuclear instrument companies pointed out what was associated with this \$5.70 potentiometer: the redesign of the circuitry in which this was going to be used, the necessity for making all the other adjustments and the engineering that had to go into this particular thing. It turned out that the \$1,200 was, in essence, a bargain.

I think you get to the point where you want to get one piece of equipment to do everything, and you can't do this. You have to face the fact too that most of the people in this field are individualists, and even though some manufacturer has made a survey and has found out what most people want, there's going to be somebody who is going to want it made just a wee bit different. This is not necessarily because it isn't usable or satisfactory the way it is, but because you want it different because you're going to use it and you want this convenient for your particular use.

With all due respect to the nuclear instrument people (who have generally done a quite creditable job), this extra convenience added for you costs money, and many times a lot of money. I think that perhaps some of the comments made against the instrument manufacturers are just a little bit unjust.

Dr. King:

I was not going to give my impression of anything, but was going to ask the panel a question, but to preface my question I will give my opinion. I think the most desirable feature of Dr. Ter-Pogossian's scanner that he had at Seattle was the fact he used an image amplifier tube and video tape readout in the storage. Now, the question I have is directly associated with the type of training we are now using in the Medical College of Virginia in our School of Medicine. Our new type of curriculum almost dictates that we use a large number of video tapes, and I think that this is going to be necessitated--whether or not completely desirable--by most teaching functions in the future.

We are putting a series of lectures, on radiation physics and radiation biology, on tape (for storage) for our house staff of all departments, as well as our students. They will be available in a teaching-type study hall with many TV monitors placed around, for evening and weekend work. The question is whether these new scanners could utilize the image amplification and video tape method of readout and storage.

Mr. Harris:

The image amplification obviously would be pertinent, primarily to the static display devices as they now embody that tube.

Of course that will get better. The business of video tape storage is applicable to essentially all classes of scanning machinery or imaging devices, provided the proper interface and readout utilization is made.

Dr. King:

You're talking about the scope now, are you?

Mr. Harris:

Yes, I'm talking about the oscilloscopic display, if that is your readout mechanism for a rectalinear device. Of course the actual means of accomplishing this right now apparently leaves something to be desired. I might extend your thought, in its whole context, to: What about more enlightened use of the information that is presently available to us from the output of the imaging devices as we now know them. So, I submit that your video tape might be shorthand for full computer interface with on-line computational facilities, and I would think that surely the next decade will see a lot more use of this. Certainly there have been a number of very notable pioneering efforts in that field. It has to come because life is too short otherwise.

Does that answer your question?

Dr. King:

Yes, it does for scanners of future design, but let's be specific and take the present scanners that are now available, other than Ter-Pogossian's. Except by taking the image off the scope with a camera, can you tie this readout into video tape now?

Mr. Harris:

Of course. I would also like to bring out another point that will come up later. One of the things I learned in moving from Oak Ridge to Duke is that while at Oak Ridge we had plenty of room and we could set an instrument in the middle of the floor and we could play ring-around-the-rosey around it and we could get at it from all angles, at Duke we don't have quite so much space. All we can see of that instrument is its front face. Almost immediately, the moment an anguished scream goes up from the scan room that this scanner isn't acting right, I practically have to disembowel that instrument to get my probe on one diagnostic point in that machine.

It should not be new to the instrument companies, as they have been told for a decade that availability of proper signals at the front panel, first of all, can assist in servicing. Our serviceman shows up, generally with a voltmeter or a can opener, I don't know which. We use the other end of the can opener to open our liquor bottle and by the time he leaves, we need it!

Secondly, an oscilloscopic device (as a pair of eyes) hooked up to the machine is the most beautiful training aid--or can be--that you have ever seen. I think Hal Anger's use of the scope monitor on his camera is another fine example of this. It's just a completely neglected and underused entity in our field. Why? Because we simply cannot get at the information.

Now, about the extra cost, Dr. Numerof--I did some looking into the economics of what is required to put a B and C connector on the aft panel of a given unit. The B and C connector costs a dollar--nobody is going to complain about that. The hole costs $2.00, and to get the hole labeled costs $3.00--now you're up to $6.00. Because of the unavailability of the significant signal information in test point form, the job of attaching a video tape to an ordinary rectilinear scanner, yea, even onto a camera, is extremely difficult because we have to practically disembowel the instrument to get our hands on the quantities. It need not be so. I got my point made, and came back to your question too.

Dr. Smith:

Mr. Harris brings up a very interesting point. I think he goes back to the basic concept of instrument design. It's designed as an integrated circuit for a particular system rather than designing a system as a modular system where you have subcomponents which you can build up into a total system, one that has great flexibility and variability.

Now, I'll get back to the question posed. The location of test points is really quite significant. There are several pieces of equipment on the market today where it takes two or three people to actually be able to get at these points on the instrument so that they can find out where the system is "down," and there's no excuse not to simplify this in the original design consideration. It would save the repairman a fantastic amount of time if he could easily find out what section of the instrument is not operating and this would be very simple to do. The situation has been, "Well, the repairmen are smart and they can find it. The physicians in the field can't be bothered with this information anyway, so why clutter up the front panel; we can always have a little thing you open up and the points are in the back."

Going back to video tape, video tape can be hooked up to most instruments, but perhaps this is not the ideal means of data output. Video tape is still an analogue signal, and I'm more visually oriented. I prefer to see information come out on tape which can be reverted back to analogue form if need be. But it's just as easy to initially record the data in a digital format so that it can be processed by a computer or redisplayed on some type of visual display. I personally do not feel that video tape is the storage medium of choice.

Dr. Anger:

I just want to echo the same comments. We have used video tape recording with a scintillation camera. All you have to do is to aim a videcon camera at the CRT output, and it's fine for seeing pictures of what goes on. If you want to get numerical data, the trouble is the TV format doesn't allow you to get accurate digital numerical data from your picture after that, so we haven't used it much.

A Voice:

As a sort of innocent bystander, I would like to ask a question, based on what I've heard today. This is a philosophic question that also is a little more related to the title of our absent speaker's talk. Apparently, at the moment, we're talking about the last decade in instrumentation, not the next one. My question deals with the next decade in instrumentation. Apparently there is dissatisfaction with current instrumentation. It has been pointed out that the engineering is done separately from the user's location, or interests, or capabilities. This morning Dr. Saenger pointed out that there is a rather limited amount of research support for instrumentation. The question then is: What is the view of the representatives of the various governmental research supporting agencies concerning the development of instrumentation by users in research laboratories; and is there, as some of my biomedical engineering colleagues have said, some reluctance to support the development of instrumentation which might subsequently have commercial possibilities?

Dr. Slatis:

Can we get an answer to that particular point?

Dr. Moore:

I'll try. I do represent the National Center for Radiological Health, and I point out that in our overall mission, the problem of dose reduction or reduction of unprofitable exposures, instrumentation is obviously quite important. I was listening here very intently because I don't know that this sort of question has arisen in deliberations where I have been and there are whole stables of lawyers who worry about the development of something that might be commercially profitable in a government lab or a government contract. Undoubtedly, there are spinoffs from this, and there are ways of handling it.

Now, the question that I would toss back is: In the next decade will instrumentation keep up with the other states of the art, other problems, so that they can go along together for the ultimate good of the patient?

I hope that somebody can tell me how many procedures are repeated or postponed because of malfunction or nonfunction of instruments.

Dr. Slatis:

Do I dare ask anybody to answer that one?

Dr. Harper:

As I pointed out earlier, the isotopes are acts of God, and the only things you really have access to to make things better, are the instruments. This is all we can work on, except of course the radiopharmaceuticals.

Dr. Kriss:

I don't think it is the last thing we have to work on, but as long as we're looking at crystal balls, which appears to have been the topic, I think that most of the speakers so far have possibly been wearing blinders. I'm not sure, but all of the discussion has been on the presumption that the instruments that we will be needing are similar to those we now have, that is the in vivo pictorial kind of representation. It is perfectly possible that this is the case. I would say it may be probable it's the case; but it doesn't necessarily follow. It's perfectly possible that the next decade will see an expansion of tests which involve radioactive materials, using in vitro systems on cultured cells, for example, in which sera or other biological materials are taken from patients and employed in this kind of fashion. Personally, I would hope that there would be a great expansion in this, and I think from recent developments in biochemistry and physiology that there is going to be an explosion in this area at which none of us apparently have been looking very seriously. If we're talking about reduction of dosage to patients, then this is the area where you're going to get it because in these instances there is no radiation given to the patients. Under these circumstances the kind of instrumentation required is fundamentally that which we already have.

If we're going to talk further about reduction of dosage to patients, then I don't think that the whole question of the training of technologists is germane to this problem at all. I think we had better begin talking about physician selection of procedure, elimination of many procedures which are now done that should not be done, and it comes back to your point. I would estimate that on this survey that was distributed this morning, perhaps one-half of the thyroid uptakes and scans could be profitably eliminated, thereby reducing materially the dosage to our population right now.

Dr. Slatis:

It's quite obvious that there were certainly problems that were raised, particularly at the very beginning (by Dr. Goodrich) that haven't really been discussed, but when you get two people from the same place down in New Orleans pointing out that one wants one type of machine and another wants another type of machine, you may have part of your problem in the fact that each of the instrument makers is trying to beat out each of the other ones at the same device, rather than one putting out his machine for the person who wants idiot buttons, and another one putting out his machine for the person who wants to be a do-it-yourselfer.

Your problem, as a group, is going to be to find out how you can put pressure on the instrument makers to make the machines for the users, so the group that wants to buy something with nothing but idiot buttons on it has it. That group isn't represented here. You are here only because you know how to work with the machines, and so you want one other instrument maker to make one that is easily repaired, has a good set of plans that goes with it (not a set of plans that can be understood by your technician, but a set of plans that can be understood by a well-trained person) and the machine especially for you. But remember the market --you are not the whole market, you are a very biased sample, otherwise you wouldn't be here. Think of the person--I operate a stick shift car, so Detroit has to put those out for me, and if you've got somebody around who needs an all automatic one, remember that they've got to have that type too.

RADIOPHARMACEUTICAL QUALITY CONTROL

Wilfred R. Konneker, Ph.D.[1]

Quality control of radiopharmaceuticals, as with other drugs, is a matter of prime concern to the manufacturer and the practicing clinician. The quality of products used for diagnostic or therapeutic applications must effectively and safely serve their intended purpose as described by their labeling.

For the radiopharmaceutical firm, the acceptance of our products by the physicians, and consequently continued growth, is dependent upon the availability of quality products at all times. The clinical user is concerned with the quality of the product which he receives in an effort to obtain optimum diagnostic or therapeutic results with maximum safety to the patient.

In addition, the increasing importance of short-lived isotopes in the diagnostic area has, of necessity, carried some of the drug production steps into the hospital, and with it the need for the hospital personnel to assume the role of quality control experts. Thus the usual mutual concern and collaboration between the supplier and user of radiopharmaceuticals has further been strengthened by joint participation in the events leading to the end use of quality products.

In our efforts to provide quality radiopharmaceuticals we are provided with guidelines from a number of government agencies. The AEC has control of licensing of users and sets standards and specifications for new radioactive drugs. The FDA presently has responsibility for enforcing good manufacturing practices and for attention to many other aspects of drug control. It will soon be assuming control of investigational radiopharmaceuticals. The NIH is responsible for the licensing of new drug products based on blood derivatives. The USP and NF, which hold official status as stipulated by the Federal Food, Drug and Cosmetic Act, set forth required quality specifications on eight of the presently established radiopharmaceuticals. It is expected that the next edition of these books will include eight to 10 additional radiopharmaceutical drugs.

The term "quality control" is customarily associated with an analytical laboratory, well stocked with a variety of equipment, instrumentation, and personnel capable of performing all sorts of measurements on drug products, and then checking these results against a set of specifications for a pass or fail decision. Actually the consistent supply of high-quality drug products starts with the initial design of the product, and it carries through all the steps of production, packaging, labeling, and testing.

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Throughout this process, dedicated concern of qualified people is required to successfully achieve a consistent high state of quality. Product quality begins in the research and development laboratory where product ideas are explored and developed.

By working closely with the clinical investigators, the requirements for the product, such as specific activity, concentration, dosage form, and other parameters, are established. Potential toxicity is considered and any necessary animal studies are run. If necessary, appropriate safety tests are then developed. The pharmaceutical development laboratory must next consider and establish suitable diluents, processing requirements, shelf life stability, physical, chemical and radiometric controls. The final form of the product must next be thoroughly evaluated in the clinic with detailed records being maintained to permit accurate analysis of the capabilities and limitations of the drug. Once the drug has been put through this gamut of development and evaluation, and finally has become a routine product, it must be manufactured and controlled in accordance with the Good Manufacturing Practices, as set forth in the regulations under the Food, Drug, and Cosmetic Act.

In most instances, the recitation of one of the government regulations becomes a rather uninteresting exercise. However, in the case of good manufacturing practices regulations, an extremely informative picture can be obtained from a review of these regulations regarding what is required and practiced for the quality control of drug products. A quick and encapsulated look at these regulations will illustrate the many facets involved in providing proper attention to a total quality control program.

(1) Buildings must provide adequate space, lighting, and cleanliness for the intended production and control purposes.

(2) Equipment must be adequate for the intended purpose, maintained in a clean and orderly manner, and must be constructed to facilitate cleaning and for the prevention of contamination of the drug product.

(3) Personnel must be qualified.

(4) Components or raw materials used in drug manufacture must be tested and controlled to assure conformity to appropriate standards of identity, strength, quality, and purity.

(5) Records must be maintained covering raw materials used, all quality control tests, and disposition of the finished material. For any single administered dose, the manufacturer should be able to trace back through the entire sequence of events to permit a review of the who, what, when, where, and how of the entire history of that lot. In addition, all other customers using material from the same lot must be readily identifiable in case a recall should be indicated.

(6) Production and quality control procedures must include all reasonable precautions to assure that the drugs produced have identity, strength, quality, and purity as specified. These precautions include emphasis on double checking, maintenance of cleanliness, identity of materials during processing, in-process control checks, checking of yields against theoretical values and a number of other details requiring constant attention and surveillance.

(7) Product containers must be checked with regard to proper specifications, tests and cleaning to assure that they will appropriately maintain the product in the desired form during shipment and storage.

(8) Packaging and labeling operations must be rigidly controlled to prevent inaccuracies or mislabeling. With radiopharmaceuticals this presents an area requiring even greater attention than with other drugs. Because of the need to type individual labels to show specific calibration times, specific activities, and concentrations of the radionuclides, labels cannot be preprinted with all of the information customarily appearing on drug labels. The potential for human error is hence increased and as a consequence this must be compensated for by an extremely rigid system of checks and rechecks on each package.

(9) Laboratory controls, written specifications, and test procedures must be developed and applied to finished products to assure adequate quality. In some instances these requirements are set by the USP, NF, NIH, FDA, AEC, or indeed very often by a combination of these. In other cases the supplier must develop, prove and apply specifications and tests himself to assure product suitability. Again, records must be maintained to show the test results of all lots of all products.

(10) Distribution records must be maintained on each batch of each drug.

(11) Stability studies must be performed on components and finished drugs in order to assure that no change will occur during storage, leading to failure of the products to meet quality requirements. Expiration dating for each product must be established accordingly.

(12) Complaint files must be maintained and each complaint must be evaluated by a competent person, with appropriate action being taken.

The listing of these major points of the Good Manufacturing Practice section of the regulations might imply that all we need to do is to know the "thou shalts" and "thou shalt nots" and then set out to enforce and police our workers along these lines. Unfortunately, it doesn't work that way. There are thousands of details which go into the handling of these matters to obtain the desired results. We not only need intelligent people attending to the details, but we also need experience and know-how as well. Again, it needs to be emphasized and reemphasized that to succeed in a total quality assurance program, awareness of the need and commitment to accomplishment on the part of all persons involved in the production and supply of drugs is essential. This can be achieved by management, carrying out a continuing educational program with respect to the guidelines, and establishing a working environment to foster concern for quality and pride in accomplishment of quality goals.

With a quality oriented organization, the quality control group then is in a good position to perform the final audit, that is, the final testing to assure conformance to the established specifications and determine whether or not a produced lot may be released for distribution. As with any other drug, the final testing is designed to audit those properties which are important to the proper clinical performance of the product and to rule out discrepancies.

For instance, the presence of free iodine in preparations of radioiodinated organic compounds is an obvious potential problem and must be checked. The same can be said for possible presence of trivalent chromium in sodium chromate solutions, ionic gold in gold colloid, molybdenum in eluates from technetium generators, and so on, with each product. In other words, the specifications and tests must be designed to fit each of the individual radiopharmaceuticals.

This is the classical approach, of course, to any good quality control testing program. However, in considering the application of routine procedures to our field we quickly find that radiopharmaceuticals as a class do indeed present certain different and unique problems. Most of these problems are related to the radioactive decay of the products, and they become increasingly perplexing as the clinical value of shorter and shorter half-life radionuclides become more and more evident.

These tests for purity of the products are in general not particularly affected by the short half-life problem. The purity of additives, such as buffers, preservatives, and stabilizers can be confirmed, prior to their addition to the product; therefore, purity considerations in the final product will usually involve three types: radionuclide purity, radiochemical purity, and chemical purity.

Radionuclide purity will, in all likelihood, have been established through raw material testing; however, repeat tests on the final product are desirable to rule out the possibility of contamination with another radionuclide during preparation. The chief concern, of course, is the presence of longer-lived contaminants with possibly longer biological half-lives. With the shorter-lived isotopes the question of radionuclide impurities can become increasingly important since larger diagnostic doses are usually employed.

The routine method for checking radionuclide purity for most radiopharmaceuticals is by the use of a multichannel gamma spectrometer. This provides an excellent and rapid method for determining the presence of significant quantities of other radionuclide impurities; however, it may fail to determine very small amounts of impurities which may still be of some significance when large doses of the drug are used. Measurements of these trace quantities of impurities can be made by permitting samples to decay through several half-lives and then examining them for the longer-lived impurities. The detection of such impurities, of course, by this method can only be made on an after-the-fact basis, hence greater quality control is being exercised on the target material used to produce the radionuclide raw materials. Activation analysis is the only technique known today with sufficient sensitivity to accomplish this job.

Radiochemical purity checks are intended to show the proportion of the total activity present in the stated chemical form. Radiochemical purity, of course, is significant with respect to the product's ability to perform the intended diagnostic test. Where the success of the test depends upon the body's handling of a specific chemical compound in a known manner, the results obviously could be clouded or even meaningless if a significant proportion of the radionuclide were present in byproducts or decomposition products possessing different biological behaviors. In most products the accepted specification is "not less than 95 percent of the activity present as the declared compound."

Radiochemical purity may be, and often is, determined by a number of methods, but chromatographic procedure is currently of the greatest importance. Both paper and thin-layer techniques are used. The USP describes several methods employing paper chromatography in its monographs for radiopharmaceuticals. The separation of various chemical compounds, by taking advantage of their different rates of travel along the paper, provides a developed chromatograph which can be readily scanned by an appropriate radiation detection instrument to show the exact amount of each item present. Typically, this technique is not without pitfalls. An impurity could conceivably move at the same rate as the parent substance, giving a false picture of a satisfactory purity. Entirely satisfactory products, on the other hand, may appear to be impure owing to the decomposition of the sample which occurs during the chromatography itself. Cyanocobalamin and selenomethionine are two examples of compounds in this category. Because of the minute amounts of the radiodrug material utilized in the chromatographic procedure reaction with trace impurities in the solvents or in the paper (or in the thin-layer material, if this is employed) can produce drastic changes, resulting in anomalies. This necessitates the extremely careful workup of a specific test system for each agent, and subsequent strict adherence to all of its parameters. More good lots of materials have been discarded because of these anomolies than I would care to think about.

The chemical purity of radioactive drug products in most cases is not a significant problem, again because of the extremely small amounts present even of the desired compound. Since with the chemical purity we are concerned with nonradioactive compounds, their determination follows classical analytical methods. For injectable products, the testing of final solutions for pyrogens, for sterility and in certain cases for safety, is important. The control of pyrogens is one of the most discussed parts of quality control of radiopharmaceuticals. This might be somewhat surprising when evaluated on the basis of actual difficulties encountered in clinical situations. Perhaps there have been pyrogenic reactions with radiopharmaceuticals, but I had not heard of them until this afternoon. Standard precautions to avoid pyrogenic contamination during drug manufacturing operations and during the use of the product (in the case of the generators) can provide nonpyrogenic drugs. Most significant is the preliminary testing of all vehicles, diluents, and concentrated bulk solutions prior to their use in the finished dosage form. Here again, the quantity of the radioactive components usually is so small as to make the question of pyrogenicity of the diluting solution or the vehicle the prime consideration. There are exceptions, of course, and the completion of the pyrogen test on the final product, prior to shipment, affords the necessary assurance.

This can be reasonably accomplished with most of the present standard radiopharmaceuticals. The situation is not the same, however, when it comes to the extremely short-lived drugs which require pyrogen testing prior to release. Technetium albuminate is an excellent example. Although it appears to be an agent of significant value in clinical diagnosis, it appears to be impractical at the moment for consideration as a commercial product. Either it would have to be supplied without full prepyrogen testing, which would be a violation of the present regulations, or the cost to the patient would be further increased from an already high level.

This set of conditions, as you know, has forced hospitals to prepare such products onsite, in order to make it possible for patients to receive the benefits of these more recent valuable advances in nuclear medicine.

It is impossible, even on today's standard radiopharmaceutical compounds (with a very few exceptions) let alone the new short-lived materials that we are talking about, to complete the sterility and/or safety tests prior to shipment. These tests require from 7 to 10 days to complete. In most cases it is not just a financial problem caused by the decay of the product over this period of time, but even more important is the problem of specific activity of the final product. The initial specific activity cannot be too high or radiation degradation will take place. On the other hand, a low starting specific activity will decay to an unusuable compound in most cases after the 7 to 10-day period.

I believe we feel that the obvious direction for radiopharmaceutical development is to the shorter half-life, low-energy gamma emitters. They allow the clinician to take advantage of the new scanning devices and/or cameras to obtain faster, more meaningful diagnostic data, and hopefully, at the same time to maintain or reduce the radiation dosage to the patient. We may all soon be faced with a value decision; that is, how valuable are these new short-lived compounds as diagnostic agents, and based on the value assessed, how do we solve these "time" problems? Can a new set of tests be developed and/or new regulations, or regulations altered, to take into account these problems--still, of course, offering adequate protection to the patient?

Perhaps the solution is to rely on the user to prepare his final product. In some cases I'm sure this is a good solution. In most I would suspect it is not. Most hospitals are now equipped to perform pyrogen tests, and I doubt that "bugs" grow any faster in hospital incubators than in ours. I'm sure there is a logical and practical solution to this problem. The potential value of these short-lived radiopharmaceuticals to the medical profession is much too great not to find this solution. It will, however, take the close cooperation and diligent efforts of the radiopharmaceutical manufacturers, the clinicians, the medical researchers, and the government agencies to accomplish this task. Meetings such as this one are an excellent place to start.

DISCUSSION

Dr. Saenger:

How many reactions have been reported to manufacturers from some accidents or untoward results of these commercially supplied radiopharmaceuticals?

I know, for instance, this spleen scanning compound or whatever it was called has been withdrawn. Was that, for example, withdrawn prior to some unfortunate experience with a patient?

Dr. Konneker:

Yes, I believe it was. Dr. Numerof, I believe you know more about this.

Dr. Numerof:

The reason why, as far as our organization is concerned, mercuryhydroxypropane is not available has nothing to do with any untoward experiences of which we are aware on the part of any patient. Our toxicologists were dissatisfied with the reported toxicological data in the literature, and we felt it our duty to provide these data to our own satisfaction before this drug is considered fit for release. We have not yet made it available again.

Dr. Konneker:

I believe the concern there was not so much the activity itself as the--

Dr. Numerof:

That is a good point. We're talking here now about mercuryhydroxypropane as a chemical and not as a radioactive material. Our concern with it was more from the point of view of this as mercuryhydroxypropane.

Dr. Saenger:

I mean, have there been other large areas of concern coming to the radiopharmaceutical manufacturers, as a group, that we might not be aware of? Since I assume you have to report these to somebody, you may as well tell us about them.

Dr. Numerof:

The point is well taken. You are quite right and you're entitled to all this information. It has been our policy that radioactivity is a poor excuse for less than the kind of quality control associated with drugs that a practicing physician has the right to expect of a nonradioactive pharmaceutical; accordingly, we instituted a procedure where all of the pyrogen and sterility tests were compatible with the physical half-life of the material; all of these 7 and 10-day sterility tests are completed because this is what you would do with a nonradioactive material. With the 6-hour half-life isotopes this is a physical impossibility because you just can't do it. You do the best that you can. With this system, to the best of my knowledge, it's possible that there could be some instances of which I'm not aware; but to the best of my knowledge we have not had any reports from anyone of any so-called drug reactions from the preparations. I think if there had been we would have heard about it.

Dr. Konneker:

We have had no such reports either.

Dr. Wellman:

I think the ^{99m}Tc albuminate is a good case in point with regard to the title of the program, that is, dose reduction. It is a very usable compound, especially for placentography, and just using it will tremendously decrease the dose the woman and fetus have to get from the procedure, either from X-ray or a radioisotopic procedure. Also, it's very usable for lung scanning, but still we can't use it because we are at an impasse as to how we're going to accept the material before we put it into a person. I mean, if we're trying to put it into the scheme that we've used for all classes of drugs, is this justified? Is there another way to look at this? We're taking a risk versus benefit type of approach to the radiological hazard. Is there a way to look at other hazards in the same way? Why are we at this impasse when we could use these things to reduce the dose and better our procedures? Would somebody like to answer that?

Dr. Slatis:

If you want to treat it as a question--otherwise, we'll treat it as a comment.

Dr. Harper:

I would like to ask Dr. Bryant Jones how he would visualize the good manufacturing practices, described by Dr. Konneker, as being applied by a user in a hospital environment to short-lived isotopes, if this is possible.

Dr. Jones:

I don't know that I can.

Dr. Harper:

We have to describe these things in our INDs, presumably so that you can pass judgment on them, and I have no feeling for what you expect or visualize, or how you would interpret these things. What would you regard as acceptable, so you wouldn't bounce back at us?

Dr. Jones:

I think you seem to have a great deal of fear about how we're going to bounce back, but I think an IND submission that contains proposals are not only for the clinical study of a particular procedure but must incorporate the manufacturing process--

Dr. Harper:

That's what I'm worried about.

Dr. Jones:

--in which you are guaranteeing a product which can be identified, which you can reproduce, and which can be given clinically to a patient with safety as a part of your investigational procedure. As an investigator, we are looking to you to develop such methods. The only method I know of in the use of short-lived isotopes at the present time, as far as sterility and pyrogenicity is concerned, is not for an individual product. I think your entire system must be under continual supervision and under continual testing, where you're testing not the final product but you're testing all of the components, and closely monitoring them all the time, and keeping the system under control rather than the final product. I don't know what more I can say at this point since I'm not a manufacturing expert.

Dr. Quinn:

Speaking to this point, as well as on the matter of pyrogen testing, there are many substances which are administered to humans intravenously which cannot be pyrogen tested because of pharmacological reactions. I speak of the barbituates and some of the narcotics. Are these exempt from pyrogen testing because the component parts in the manufacture are controlled and pyrogen tested, and yet the final product cannot be? I don't think 20 cc of Nembutal in a rabbit is going to cause much of a febrile reaction.

Dr. Meyers:

I knew I would have to get into this sooner or later. I think there is a misunderstanding on pyrogen testing and sterility testing. It's only a part of the overall picture, and I'm afraid a small part. It is a presumptive test either way. When you consider the rabbit (it's the best we have on pyrogens), it doesn't tell you a lot. When you consider 10 or 20 units for sterility, it says those 10 or 20 subdivisions are sterile or not sterile, and this is about all it says--they're presumptive tests.

It's not just radiopharmaceuticals that we are concerned with, it's across the board, any injection. You start out with the raw materials from which you are going to make a product that you're going to put into a human being. You're going to inject it, and you have to keep that in mind all the way through. There are many products that we can't test for pyrogens in the rabbit. What do we do? We rely on the materials, the water, the sodium chloride, etc., so that whatever you have is pyrogen-free before it goes into the product making up the formulation. Then you protect it all the way through. This is the best you can do. We may have to come to that on radiopharmaceuticals.

The same is true for sterility. You set up an empirical fashion of processing and you guard it all the way through, and you check that empirical process by using other means. You put in bugs and test them (not in the radiopharmaceutical, but in an accompanying vial or vials) to see that your system, your autoclave, your pressure cooker, or whatever you have, is working, that the whole system is working, and then you rely on that. You cannot test many of these short half-lived materials. You can take some extra ones, make them up at the same time and test those, but I have seen some--and I shudder at this--take a little out of a vial to test for sterility. I'm not sure, but they might have contaminated the vial in making their test. So, again, these are presumptive tests, and we rely too much on them the same as we do on some of the assays. We must feel all the way through that we're making pharmaceuticals to give or inject into a human animal, and we must keep that in mind and protect the product all the way through. Then we can quit worrying about some of these tests and whether we can make them or not.

I don't know if that answers your question or not, but this is what we do with other pharmaceuticals. I don't know why we should get so particularly concerned about radiopharmaceuticals. They're drugs, they're the same all the way through, and if we think along those lines, I believe we will get over some of these barriers and come up with good manufacturing practice and good drugs for the human.

Dr. Slatis:

One last short remark.

Dr. Kuhl:

I think we should maintain a proper perspective in summary of all this. I think the radiopharmaceuticals have a fairly enviable record up to this point, and if you look at an analogous situation with the radiopaques in radiology, there is a known morbidity and mortality rate as a side effect of these, but we continue to work with them and to accept this in the same category. I think that in actuality we haven't done very badly, and I think, as Dr. Meyers has pointed out, that radiopharmaceuticals should not be considered any differently than anything else.

TRAINING AND MANPOWER DEVELOPMENT

William H. Beierwaltes, M.D.[1]

In our clinical units today, the Chief of our Clinic, for one-half day, decides whether a given patient should have a test using a radionuclide. He selects the radiopharmaceutical that he thinks will be best for each test. He decides the dosage (the radiation dose to be used for that particular patient), and lastly he selects the instrumentation that he thinks will get the best data in the shortest period of time. Therefore it seems logical to me that the most potent single tool in decreasing radiation dose today is an intelligent, well-trained, thoughtful physician in this field of nuclear medicine. From the general observations of technicians sent to us for training from doctors in practice around our State and other States, perhaps 90 percent of the hospitals in the United States--at least the small hospitals--do not have a physician who is doing this. As a result, a technician is making these decisions. I think the point should not be forgotten, however, that this is practice by default. It's going to be a long time, if ever, before we have intelligent, well-trained, thoughtful nuclear medicine physicians in all hospitals with a Nuclear Medicine Department. Perhaps we will have to concentrate on technicians in the interim.

I first want to talk about need. Mr. Van Farowe of our State Department of Health--I can't remember exactly when this was, but I think it was this spring--told me that we had 302 active medical licenses for radionuclide use in the State of Michigan. This gives you an idea of how many different radionuclides or licenses for radionuclides are operative in the State of Michigan alone.

In a survey that I did some years ago of hospitals with zero to 300 beds, 300 to 600 beds, and greater than 600 beds, we found that 79 percent of hospitals with a hundred beds or more had radioisotope units. We then checked the American Hospital Association guide and found how many short-term general and specialty hospitals there were in the United States with a hundred beds or over, and we came to the conclusion that 79 percent of these, or 4,375 hospitals in the United States, needed a man to run their radioisotope unit. What percent of these positions are actually filled by a physician on the spot, I don't think anyone knows. Dr. Moore, I think this would be a good thing to find out by some good questionnaires.

The further details on this are furnished in an article I wrote at the request of the Student American Medical Association in their journal, The New Physician. The article, entitled "Your Future in Nuclear Medicine," is published in the June 1967 issue.

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I don't know what the need is in university hospitals for men to head up nuclear medicine sections or departments, or other places where these men will be trained. I can tell you, however, that we have averaged about six current requests from various university hospitals, asking us for any man who's been with us for 1 year or more, to head up their nuclear medicine section or department. The going salary on about the last six or seven offers was $16,000 to $22,000 a year, and one of my men who has not finished his training was just started at $30,000 a year.

Who are these people who are manning radioisotope units today? I don't know who they are for sure, but the details of the survey that I made a few years ago certainly are compatible with Dick Peterson's analysis of the membership of the Society of Nuclear Medicine. At this time the physician membership in the society of Nuclear Medicine is doubling every 5 years and this is the breakdown: radiologists, 44 percent; internists, 30 percent; pathologists, 22 percent; and the most recent increase has been in doctors of osteopathy, and pathologists.

Now that we have discussed the need in manpower training, let's talk first of all about the definition of nuclear medicine. This definition was agreed upon by the Board of Trustees of the Society of Nuclear Medicine, and is now being circulated in the Journal of Nuclear Medicine for final approval. The definition of that group is: "Nuclear medicine is that scientific and clinical discipline having to do with the diagnosis, treatment and investigation of disease with radionuclides, exclusive of sealed radiation sources."

Another way to define nuclear medicine is to look further to the Advisory Board of Medical Specialties of the AMA and their Directory of Approved Internships and Residency. They define what is a subspecialty and what is a specialty; and we all agreed that nuclear medicine comes under the heading, not of a subspecialty, but as a specialty under "broadly useful methods of diagnosis and treatment." Of course, we all expect that it will be much more broadly useful as we develop new imaginative uses that will have the same importance as, for example, brain scanning.

Another way to define nuclear medicine is actually to show in somebody's unit what the actual practice of nuclear medicine consists of--and here, of course, we're taking ours. We see 7,400 patients each year, and 98 percent of these visits are for diagnosis. These diagnostic uses fall under four headings: (1) volume or quantity determinations; (2) function tests; (3) scans; and (4) point counting. We have breakdowns by percent for each test, and the number of visits per year for each.

Under therapy, this comprises only 2 percent of patient's visits. We average 90 patients a year for the treatment of hyperthyroidism with ^{131}I, which has now totaled over a thousand; thyroid cancer, 30 patients a year (these are new patients each year). We have totaled now 300, and in our personnel meeting held last

Thursday noon, they told me that we were averaging two thyroid carcinoma followups a day, 5 days a week, 52 weeks a year; and 28 patients were being treated with ^{32}P for polycythemia.

That helps define the duties--or what nuclear medicine actually is.

To the best of my knowledge, this is nuclear medicine as it's practiced (at least in our hospital), and thought of from the standpoint of the Society of Nuclear Medicine.

So much for need and definition. Now let's go on to actual training requirements. The present AEC requirements are as follows:

A. GENERAL TRAINING IN BASIC HANDLING TECHNIQUES

1. Radiation Health Physics
2. Radioactivity Measurement
3. Mathematics and Calculations Basic to 2
4. Radiation Biology
5. Experience in Use of Radionuclides

B. CLINICAL RADIOISOTOPE TRAINING

1. Examination of Patients--for Diagnosis and/or Treatment
2. Dose--Calibration, Administration, and Follow-ups
3. Management and Follow-up After Dose
4. Study and Discussions with Histories

CATEGORY I: DIAGNOSIS

1. Thirty Hours of Basic Training
2. Perform 5 Uptake Studies
3. Perform 3 Dilution Studies
4. Perform 3 Excretion Studies

CATEGORY II: SPECIALIZED DIAGNOSTIC PROCEDURES

1. Thirty Hours of Basic Training
2. Perform 3 Tumor Localizations or Organ Scans

A few years ago when I was President of the Society of Nuclear Medicine, the officials from the AEC consulted with us and asked for consultation on a couple of problems. I asked Dr. Merrill Bender if he would be our chief consultant for their use. It became apparent to Dr. Bender that the problem of risk versus benefits included efficacy. Efficacy, to a certain extent, depended upon competency of the physician (which was my introductory statement). If the competency of physicians in this area was very poor, it is easy to understand why there would be some reluctance to release a drug to improperly trained people or technicians for example--this might slow new drug development. If new drug development is slowed, certainly the progress of nuclear medicine will be slowed. Dr. Bender became particularly concerned with the problem of competency. We had been concerned with this for some years in the Society of Nuclear Medicine and had been steadily plodding along developing some credentials for competency. We had a special meeting of the Board of Trustees of the Society of Nuclear Medicine this spring. We had some preliminary agreements which were then brought up before the Board of Trustees of the Society and they were agreed upon tentatively. They are to be circulated in the Journal, and hopefully agreed upon formally by the Society by the end of the year.

We took the AMA Directory and prepared a guideline statement of eligibility and training requirements for physicians in nuclear medicine. This was based upon the assumption that nuclear medicine will eventually qualify as a specialty under the AMA recognized rules of "broadly useful methods of diagnosis and treatment." We made a decision on each of the prerequisites that the AMA lists.

Prerequisites: (1) U.S. citizenship is not required; (2) candidate must be a graduate of an AMA-approved medical school; (3) he must be licensed to practice medicine at the training site; and (4) candidate to have 1 year of internship, or equivalent.

Residency requirements: we decided on 3 years of training as follows: (1) 6 months in nuclear medicine basic sciences; (2) 30 months in general clinical nuclear medicine; and (3) at the discretion of the examining body, up to 12 months of the clinical nuclear medical training requirement may be met by: 12 months spent in investigative nuclear medicine or 12 months spent in a related clinical specialty such as anaesthesiology, internal medicine, pathology, pediatrics, radiology, and surgical specialties. Initially, there should be no practice time requirement before eligibility to take a written and/or oral qualifying examination which may be established.

Dr. John Lawrence asked that a committee of the past presidents meet and make recommendations to the Bylaws Committee of the Society to establish a Credentials and Certification Committee, the function of which is to offer service to members of the Society of Nuclear Medicine, and others, by judging competence in nuclear medicine on the basis of credentials and/or examinations for the purpose of designating clinicians as qualified specialists in the discipline of nuclear medicine. We felt that by setting this up as a specialty with some competence, it would stimulate further training and excellence on a wider scale in the field of nuclear medicine.

Since there are no actual residency programs in nuclear medicine anywhere, an interim solution to this problem is the program of training grants. There are at least two in the National Cancer Institute, and a much larger number in the Division of General Medical Sciences. Our present plan, on our own training grant in nuclear medicine, is as follows:

MONTH 1 - Course for residents.
MONTH 2 - Assist in teaching course for residents (full time).
MONTH 3 - Assist 2 half-days a week.
- Select and start clinical area of responsibility.
- Select research mentor (read research proposals and have interviews with mentors).
MONTHS 4 through 12 - Continue as in 3 and take 2 hours of seminar each week.

First, the man, during his first year, starts out with our 1-month course (which is given 12 months a year); this applies to every resident of the department of medicine, radiology and pathology, and occasionally for obstetrics and gynecology; secondly, during the second month, he assists, full time, the principal teacher in our unit in teaching the course to residents; the third month he assists on two half-days a week in this teaching. He may be chief of the clinic on those two half-days a week, usually with a senior staff man. Then he selects and starts his clinical area of responsibility. All of our tests are covered by a junior or senior man. For example, one may may be in charge of the kidney, another man the liver, and so forth. The trainee selects the clinical test area that he will cover. He starts to select his research mentor, reading research proposals of the staff, and having interviews with mentors, and rotating through their laboratories. He continues this during the months 4 through 12, and in addition he starts to take seminar courses each week.

We feel that our seminars are as important as the basic course work. Dr. Knoll holds a Ph.D. degree in physics; he's a professor of nuclear engineering and is interested in radiation detection instrumentation. He teaches a 6 weeks course for eight students, both lecture and laboratory, in nuclear engineering. Beaver Thomas is a former trainee who's now an instructor with us. He assists on this instruction on instrumentation. Chuck Rose is a radiation health physicist and teaches radiation health physics and dosimetry. Dr. Claire Shellabarger gives the seminars on radiation biology. Al Saadi teaches cytogenetics, and he holds a Ph.D. degree in zoology. Dr. Weinhold holds a degree in biochemistry and we are interested in having him join us during his second year of a postdoctoral fellowship at Harvard. He teaches concepts of metabolic pathways leading up to radiolabeled pharmaceuticals. Ray Counsell has a Ph.D. degree in pharmaceutical chemistry. Ed Carr has been in nuclear medicine for many years. He is now chief of clinical pharmacology. He teaches a course in radiopharmacology. Then the junior and senior staff teach one session each on their core clinical coverage--the core clinical coverage is pretty well outlined by the survey that's being done by Stanford.

It's of interest to me that when we sent out a brochure to prospective applicants for training, covering these points, many people wrote in and said, "I'm not interested because you don't seem to have anything clinical." I think this is an important point, that the average applicant for training in nuclear medicine is highly clinically oriented and you must stress the clinical opportunities available. We then had to send out another brochure actually detailing what the clinical opportunities were.

One of these opportunities is of special interest, the "specialty conference." For example, the man who's in charge of kidney studies meets weekly with the conference on hypertensive renal disease with the urologist, the man in charge of hypertension, the medical renal unit, and so forth. This gets to be very important to the trainee, and eventually he may end up doing research with the renal physiologist from the department of physiology. This seems to be particularly important in increasing his competence in a certain clinical area.

I want to stress that it is difficult recruiting physicians today. There is a lot of competition and there are too few medical schools (for the population) to produce enough doctors to take care of all the various areas that need care. Our program had just reached the place where we had more applicants than we could handle when Vietnam came along. Then the armed services stopped almost all of our incoming applicants and took two of the men who were already in training. Other possible applicants all say that they have a deferment at NIH. Also, AEC pays more than we're allowed to pay--$13,000 to $16,000 a year. However, our specialty is too new and not sufficiently developed to attract men on a broad scale. When we have 10 more tests like the brain scan, we will attract men regardless of all the competition from other areas--if there are enough doctors to attract.

At the Training Grant Directors' Meeting in Palo Alto, it was of interest that everyone arrived at the same conclusion (which I think is applicable here), that we have to go for the men, for recruiting, on at least four levels. These are the premedical student, the medical student, the intern and the resident, and the older man who has finished training, or is out in practice, or decides that he wants a different specialty.

We have two great problems: the first is attracting the men by having "resident pay" available, if he's going to have a residency. This money is not available because to my knowledge there are no residencies in nuclear medicine. The hospital will not allow us to pay a resident in nuclear medicine, nor will a training grant. The second problem is that the older man really needs a $14,000 scholarship.

The surveys that have been done on the training opportunities are completely inadequate. Here again, the National Center for Radiological Health might help.

The American Medical Association conducted a survey in early 1967 on the formal courses in nuclear medicine for physicians. They found that 23 courses were offered in 10 States and only 12 cities. A similar survey by Dr. William Maxfield showed that 38 States, 108 cities, and 170 institutions offered formal courses in nuclear medicine. Dr. Maxfield commented that it is very difficult to know whether this is just for physicians or also for technicians. There may also be some duplication. These courses are usually of the type that qualify the physician for the present AEC licensing.

DISCUSSION

Dr. Harper:

Under what part is the in-patient service you mentioned?

Dr. Beierwaltes:

These are in-patients from any service that our resident cares for. Under the formal setup in our internal medicine department, we cannot have patients under our own jurisdiction.

Dr. Saenger:

I would like you to amplify a little more on the proposed training program for the specialty of nuclear medicine. What is in a proposed 30-month training program for a man in order to be certified eventually in nuclear medicine? The program you defined was for somebody who has completed his residency in any other field.

Dr. Beierwaltes:

This is not a problem for us now because, of course, we only have funds available for training and research. The program is for an internship plus a year or residency. We are down to 1 year of residency, but so far all of our men have had 2 years of residency in some field.

Dr. Saenger:

They have to have more clinical preparation of some kind. Do most of your people come from internal medicine?

Dr. Beierwaltes:

The most recent one that we have had finished 4 years of radiology, he just started July 1. We prefer that type if we can get them--I don't mean specifically a radiologist, but I mean that we like to have someone with an internship and 3 years of residency. However, right now there are probably 4,379 of these people needed. We're not trying to fill those; what we're trying to do is to train men to set up centers to train men. There's some spinoff because every once in awhile we get a man who believes (and we agree with him usually) that he's not equipped to have an internal medicine position in a university. Then he goes out to a fairly good-sized hospital where he may train men to go to smaller hospitals. But when the residency does come along, I think that at this stage your best opportunity for teaching disease in depth will come from the type of association that departments of pathology, radiology, and so forth have--namely, with the specialty clinics. For example, the renal clinic or conference once a week (if he attends that) to decide which patients have renal hypertension, and then he attends the brain conference the next day, and so forth. He does this every single day, and he's going to learn a great deal about general medicine, particularily if he actually gets in there and participates with them. But the day will come when he will have a widespread application so that it will be all you can do to learn just the medicine related to this field during a period of 3 years.

Dr. Kriss:

I think one of the most important things I have learned so far in this meeting is: First, that technologists apparently are conducting tests without either proper supervision or in some instances apparently without any supervision, and the second point is the magnitude of this problem (as brought out by your figures) that would indicate that something like 4,000 physicians are needed to fill positions in those laboratories that are unmanned from a physician's point of view.

What I would like to know is: What is the legal status of these laboratories throughout the country? Are there differences in State law, for example, that would permit you in Michigan to operate this way and those laboratories in California not? If these are illegal, why do they exist?

Dr. Beierwaltes:

It is really worse than that. One of the most fascinating questionnaires that has been returned was from a hospital director (and other officials) who saw actually nothing wrong with making it clear that a man who has a master's degree in physics, diagnosed and treated patients and did other things in the units. They saw nothing wrong with it, they were glad to admit. What really startled me was that they put this down in writing and sent it without any feeling of guilt. But in all other instances, I think if you would go at it legally you will run into a blank wall because they would say, "Dr. Jones is in charge of the radioisotope unit." You would then have to go in and say, "Well, I'm going to stand here and see him, see that Dr. Jones is here, and exactly what he does." That would be an entirely different story.

Dr. Kriss:

What you're saying is that they're operating under something like a paper figure? There's a name in charge, but there is not an actual physician operating it?

Dr. Beierwaltes:

I think this is a wide spectrum. How many hours a day is every doctor in every radioisotope unit supervising everything? I think if you went to every laboratory you would find a wide range of differences. Some doctor might be doing every single task, doing everything all by himself without any technicians--I'm sure that's true because I know of several instances where that's true.

At the other end of the spectrum, perhaps even the technician is deciding doses--therapeutic doses for all I know.

A Voice:

Dr. Kriss, actually I think the point is that all the departments that Dr. Beierwaltes is talking about have licenses issued to individual users. whether they are on a State basis or a Federal basis. The individual has simply become indolent, either because he's busy, or because he doesn't care and so he is letting the laboratory run this way. It's a personal problem, but there is one man, one physician responsible even where he is just reporting results. I think this is where the problem arises. Perhaps this is a good reason to tighten up the regulations so that these individuals, that are so loose, can't be licensed.

Dr. Cloutier:

It hasn't come up today, but I am sure most of you are familiar with the training program at Oak Ridge. There are something like 6,000 students who have gone through the special training division. They are set up only to do training programs. They run five medical courses each year, and I would guess that a large number of physicians that now have licenses have gone through that program, because at the time the program started there were no programs at the universities.

I think we are moving in the direction of the year program, but I still see a large number of physicians coming to take a 3-week program or 4-week program. With many of them, the radioisotope work is a prime function. They're located some distance from a large medical center, and yet they would like to make use of such things as even the T-3 test (which shouldn't require much training) or the thyroid uptake. I think there is a need for training that is perhaps much shorter than the type you're talking about.

We did run a training program last year for technicians, and if there is a need for trained technicians it is hard to find, because I know that up to the date our course opened we were calling up people asking them if they had any technician that would come. They all had some excuse, either the technician couldn't leave the laboratory for fear that the laboratory would fall apart, or they couldn't afford to invest in technicians because most technicians are girls. The girls will be getting married, and then will become pregnant, and if they get pregnant they can't work with radioisotopes, and things like that. I am a little concerned whether it's a technician-training program we need after they first start working, or whether we need a technician program in the junior colleges as we discussed before.

Dr. Beierwaltes:

Our experience, of course, is biased, so I'm not sure that I have any evaluation of the results of your training. We have a postgraduate course of 1-month duration, and have had since 1954. It is a formal enrollment in the Department of Postgraduate Medicine for 12 months a year, and the physicians who still come to us in that course now come to us for one of two reasons. They say, "I've been to Oak Ridge, I've got all that basic stuff, but now I want some patient experience, and I'll come with you for a month." Secondly, we always have a waiting list of technicians that want to train with us. The doctors say, "I want my technician to work in a nuclear medicine unit which is roughly comparable to what she will have when she comes back here, and I want her to be brought up-to-date on the latest things. She's had some basic training, but I want her now to be brought up-to-date on the latest in a busy unit." They all speak very highly of the Oak Ridge course, and they never find anything wrong with it, but they feel that, if they have experience where there are 7,000 patients a year being seen, it would be more comparable to their own situation when they get back--it's the final touch.

Dr. Goodrich:

I would suggest that rather than there being no technician need, there was instead a lack of publicity about the training program by the Oak Ridge facility. There was no advance notice of any program sent out, and I heard about it at a meeting quite by chance.

Mr. Harris:

I am a little bit disturbed at Gene Saenger for being so concerned about the residency requirements that you read. I think it is very easy, perhaps even for those of us who were at that meeting, to get that a little bit out of context. As I remember, there was a statement of what would be the ongoing residency requirements once an examining board--a specialty group of nuclear medicine--is established. Just 30 months of clinical nuclear medicine sounds awfully disorganized, but I assure you that in Dr. Beierwaltes' place, 30 months of clinical nuclear medicine is a great deal more organized than that. Indeed, in our place, where we have no such counterpart, we at least try to rough it out on paper just to see what would happen if tomorrow we could get our hands on some input for a residency program. I think we must put the cart in front of the mule before we're going to have any input.

I think another very pertinent point is that right now we are sort of self-protected by an unwholesome situation. We have two young fellows coming in on the rotation with us in October who want to do nuclear medicine full time. They are tolerating a residency in radiology to get to us--because at Duke that's the way you get into nuclear medicine. While we have this anomalous situation of people tolerating a 3-year residency to get 3 months of nuclear medicine, they're learning a lot of medicine on the side, and it's good. But somehow we've got to get from now to then, protect the interests of this group, and at the same time start getting some valid input.

Dr. Saenger:

The way I feel about this is that I question whether training just in nuclear medicine constitutes--with the limited number of diseases actually handled--an adequate preparation to a man who would have to have a wider experience in the future, and I think even to those of you who might be in internal medicine rather than radiology. Even with the experience in diagnostic radiology considerably broader, in my experience there is very little opportunity for a man in nuclear medicine, as most of these training programs are set up right now. Maybe there will be some great breakthrough in nuclear medicine, but even then we're not getting patients in the general medical service, but patients who get rather esoteric studies.

A Voice:

There's one thing we talked about before (but not here today I believe), and that is that we've got to get back even to the medical school itself. We've got to get nuclear medicine into the curriculum some place so that we will have the feedback to bring the boys on up into this and make them interested. Once they're interested, then once we can do this--I don't know how we're going to do it--

Mr. Harris:

Into how many medical school curriculums have you been able to get some nuclear medicine curriculum in the last 5 years?

Dr. Workman:

I'm ashamed to admit we had some but we lost them.

A Voice:

I was wondering--I shocked a number of technicians who visited our lab and who would come in and say they're doing all the work each day; they're injecting the isotopes, and so forth--when I asked them how much malpractice insurance they've got. Why they don't know that they are liable when they inject I really don't know.

A Voice:

They're not, that's the trouble. The lawyers are not interested in the technicians.

A Voice:

The physician is liable, but just to shock them into the situation that if they do injections they can be liable, but they can be bonded to give injections. The point is that on most wards the nurses cannot give injections. What I am wondering is--in this whole training process of technicians and physicians--where does this break down, getting this information across to them that these are pharmaceuticals, and they they should be injected and handled by physicians and not by paramedical personnel?

Dr. Beierwaltes:

In our unit no one is allowed to inject a radiopharmaceutical except a physician.

A Voice:

I think it is fairly rampant, and the technicians are doing this.

Dr. Kuhl:

I think that we ought to face the fact that in the future it is very unlikely that the physicians are going to be spending their time injecting radiopharmaceuticals, and I think that in the future we're going to find nonphysicians doing barium enamas, upper GIs, and other things. We don't have enough doctors to go around, and the doctor's time is ill spent in giving radiopharmaceutical injections routinely. I think that what we should be spending our time on is properly educating these people who are going to be spending their time giving the injections. It should not be some ill-educated technician. I think a properly educated registered nurse is the proper person to do this.

A Voice:

I would agree on this. But why should the physician inject, what is the sense? Well, the point is that if something happens, and the patient does have an anaphylactic reaction, et cetera, he knows what to do about it.

Dr. Kuhl:

A physician should be available; there should be a physician in proximity.

Dr. Beierwaltes:

Actually at Duke they have set up a course in the medical school to train paramedical personnel for the exact function you're talking about. It is a special course for a man who is not quite a doctor and not as ill-trained as a technician.

Dr. Maxfield:

I think there is one point that should be made on this problem of injection. There are many substances that we use all the time that are injected by other than doctors, that are much more dangerous than the radiopharmaceuticals that we use. This last week I spent 2 days in bed because I got an overdose of my allergy shot by mistake, a 10 times dose of ragweed allergy kind of put me out for a time. This is the second time this has happened, and I'm quite aware of this problem.

Dr. Slatis:

Obviously somebody has been touching on a sore nerve around here. Are there any comments that you have been sitting around with for an hour or so that have to come off one way or another?

A Voice:

I want to go back to the instrumentation for just a moment.

Dr. Slatis:

Go ahead.

A Voice:

I think that one thing Dr. Ter-Pogossian might have mentioned, and that some people alluded to, was the use of computers in scanning instrumentation in the future. It is quite reasonable that some are planning to do this, to bypass everything from the pulse height analyzer on, as we presently know it, and to go directly into a computer on-line. This can not only save money but it can cause a tremendous cutdown on technician errors, because there is no longer any CRT tube to set. I believe--we are trying, though we have not proved this yet (but we hope to soon)--that we can actually increase the resolution that can be achieved with the scanner, and thus cut down on the doses that are necessary, or decrease the time of scanning that is necessary. I think that in the future most scanners will be attached directly to a computer of some type. The question is whether it is going to be a special-purpose computer, like the one with which Dave Kuhl is working, or the one that Picker is producing, or it might be a large, multi-purpose computer which is the approach we have been taking. I am sure computers in the future are going to play an important part in reducing radiation exposure.

Dr. Harper:

This is part of the general question of data processing, and I don't think it should be limited to computers exclusively. I certainly think this is one of the big directions--I don't think it's going to be a breakthrough here, but I think there's going to be a substantial advance.

Dr. Slatis:

I think it only fair to tell you that when I was going to school they told us that by 1965 all this sort of work would be done by computers, and I'm looking forward to it.

Dr. Goodrich:

I would like to address myself to Don Brown and to Dave Kuhl. I traveled for several years, touring and seeing the computer displays and looking for something that would give me a means to make a diagnosis of a brain tumor that was smaller than 2 or 3 centimeters, or to tell me that this was a tumor instead of a vein. So far, all I have seen, really, are some very elaborate displays of this equipment. They do a good job of showing lesions that you could probably hear, and then producing it in such a way that it was at least as good as a photoscan would have been if it had been properly done in the beginning. This is very critical, and I'm going all the way overboard, but it just would be nice if they would show us something we can't see on the primary image.

Dr. Smith:

I would like, first, to address a comment to Dr. Brown. I think a computer is wonderful, but here you're taking a mechanical scanner and its associated electronics and another electronic monster which is known to break down. I think if you try to multiplex these two devices with some type of intermediate data storage you're in real serious trouble, because your entire lab can be "down" because of one piece of equipment. There is the multiple probability with various pieces of equipment, in that if one of them breaks down, the whole thing will be out of order. The one comment that I would really like to make is that you must have intermediate hard storage when you have positive data.

Now I would like to direct a comment to Dr. Goodrich. I agree that these analogues, these visually processed analogue displays, are great, and they are very useful if you apply them to the numeric data that you can get from your scanner information. If you superimpose your numeric data on top of these digital data-process analogue displays you can get a significant amount of information; and I think we're now demonstrating this, especially in the area of renal studies, *et cetera*. You cannot use the analogue display you get out of that scanner in the same way as the computer.

Dr Kuhl:

Some times all of us who are here in this room are accused of being preoccupied with scanners and computers, and so forth, in nuclear medicine, but I think (to be a little philosophic about it) if we look at what it is that really characterizes nuclear medicine, we can say it's the tracer method. If we look for a single instrument that may characterize the field 20 years from now, I think it will probably be an imaging device. The reason that I say this is because the tracer method with which we can measure precisely extremely small amounts of material, and the thing that is most different about our clinical specialty is that we can make our measurements from outside the body. Also, with a scanner we can orient these things spatially, and tell in what part of the body they are located. If you put all these things together it makes a picture and gives quantitative information about it, and 20 years from now if the field still survives all the symposia, this will be the instrument that will be used.

A Voice:

Just to reopen another subject that was mentioned earlier--this is a comment about something Bill Meyers mentioned. He said that we should switch in our thinking from the rad to the rem, especially when we talk about the philosophy of a safe dose, and so forth. I think the time-dose relationship of this deliberate dosage should be brought up in the philosophical sessions that I anticipate tomorrow. This has never been stressed in any of the literature on radiation doses, and I think this is a very pertinent factor about which people in radiology have been well aware.

Dr. Harris:

I would like to, clarify one point with regard to our earlier discussion. We were chided a little bit for dealing with the past decade more than we dealt with the future decade. I can summarize my feelings by saying that one of the things I would like to see come in the next decade is something that could have been done in the last decade. I would like to see nothing more than the quality that can be had with a reasonable expenditure of funds--something that is now abundantly available in nuclear physics--radiochemistry laboratories; Oak Ridge National Laboratory has good equipment in abundance, some of it no younger in philosophy than 1958 or 1959, and I would just like to see that much available to us now.

A Voice:

I have a question for Dr. Beierwaltes since we're talking about the next decade, and the specialty of nuclear medicine during the next decade. I wonder if there is any place for the diagnosis and treatment of radiation injury as it emerges from our growing nuclear industry, certainly a reality in the area from which I come. It is excluded by your definition and your training, and who is it that takes care of the contaminated, injured patient

--contaminated with radioactive material? The radiologist is not trained, the internist is not, and you're excluding this from nuclear medicine.

Dr. Beierwaltes:

Well, I didn't mean to exclude it, but I guess what we're really worried about is the radionuclide getting into the person. The radiation incidents that we have had (and we do handle them for the hospital by the agreement of all the specialties, and also for the State of Michigan) was merely contamination of the skin. However, we have always wondered whether significant amounts were absorbed, and so forth. We have entered into that from a diagnostic standpoint, but the conclusion, so far, fortunately has been that no one has really received an amount to really worry about.

A Voice:

Would you consider this part of the practice of nuclear medicine?

Dr. Beierwaltes:

We do, but you know we have only about one a year. The ones we see we have to do something about from a legal standpoint with the university or a nearby corporation. There are some corporations nearby that ask us to see any patient where it is suspected.

A Voice:

I wanted to add that in the 1-year program at Oak Ridge (I was there 4 years ago) we did spend a fair amount of time discussing this, and I think the people who go through that program will all consider that it is part of the curriculum. It is rather informal, but certainly much better than most radiology programs.

Mr. Harris:

Other than Oak Ridge and possibly Brookhaven, do you know of any place that gives this training? I assume this is what you're alluding to, to acute and subacute radiation.

A Voice:

You don't have the clinical material fortunately to work on; but I think Dr. Beierwaltes's students surely will be prepared for this, don't you?

Dr. Beierwaltes:

Yes, they are. There's human radiation biology which includes the acute and chronic radiation syndrome--that's part of the training.

EXPECTATIONS OF THE PUBLIC REGARDING PHARMACEUTICALS

George F. Archambault, Pharm.D., LL.D.[1]

It is indeed a pleasure and a privilege for me to join with you in this symposium dealing with the reduction of radiation exposure in nuclear medicine.

I suspect the reason for my being on your program is the fact that I have dual practice rights--law and pharmacy. I am a member of the Bar in the State of Massachusetts and licensed to practice pharmacy. In addition, I am a bit familiar with the public's expectations of those involved in the medication distribution process, by virtue of my close association with the Office of the Surgeon General of the U.S. Public Health Service for the past 15 years.

To present my credentials--or lack of them--for I have no "expertise" in your area, I would point out that for the past 15 years I have been serving on the faculty of the Law Institute of the American Hospital Association. This faculty gathers annually in different cities in the United States, for the purpose of updating hospital administrators, trustees, and attorneys as to the new case and statutory laws that have evolved during the year, as well as a general overall review of this specialty field of law. My assignment with that group deals with the Law of Medications or Drugs and Pharmacy Service, as such laws and codes relate to the institutional setting.

My subject assignment this evening, "Expectations of the Public Regarding Pharmaceuticals," as you may have guessed, will be in this legal context. It will be confined for the most part to tort and criminal malpractice negligence as this relates to medications in the clinical or investigational trial status. I suspect that much that will be covered will be but a "Bringing of Coals to Newcastle" to many of you.

To move into the subject, let's ask ourselves a question and then attempt to answer that question. The question, "Just what does the public expect of medications and what has been done to meet this expectation?"

The answer to "what is expected" is fairly obvious--the public expects medications that are safe and efficacious for the purpose for which intended, when administered or used as recommended.

As to "what has been and is being done to assure this," let us turn back a few pages in time and move on up to the present and see what there is to see.

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Around 1900, several children were killed in the St. Louis, Mo., area as a result of the administration of a diptheria antitoxin produced from the serum of a horse ill with tetanus. Result - a few years later, about 1902, as one of the first National acts resulting from the public's expectation that medications be safe and effective, a Federal law was passed that created what is today the Division of Biologic Standards of the U.S. Public Health Service. For 65 years now this Nation has had a splendid record of safety in the area of biological drugs--only one large failure - in the early days of the polio vaccine; the standards were not as they should have been, and the tragic Cutter polio cases resulted.

As an aside, let me point out that this manufacturer and distributor was not found negligent by the court, but rather the cases were decided against him in the framework of contract law, the law of sales, on the grounds of an implied warranty of fitness for use as applied to "items inherently dangerous."

One might ask, why did not Congress, in 1902, move for standards for all medications instead of biologicals alone. The reason given at that time was that Congress and others were of the opinion, inasmuch as the other pharmaceuticals could be tested after manufacture, that no such urgent need existed for controls over them as with biologicals.

However, some 4 years later, in 1906, an overall Food and Drug Act came into being as Congress did begin to recognize the need for some control over all medications and food substances. The pioneering work of Dr. Wiley and women's organizations, again the public's expectations, had much to do in giving us this beginning of Federal monitoring of drugs or medications. Only the more obvious harmful medications in the O.T.C. category were encompassed at that time and "legend drugs" as such, were unknown.

This country then coasted along for some 3 decades until 1937, when the Elixir of Sulfanilamide tragedy occurred. This was a case where a drug firm used as a sulfanilamide vehicle, a solvent, one not poisonous in 1 or 2 ml doses, but lethal in larger doses--diethylene glycol--and 107 lives, mostly those of children, were snuffed out.

Incidently, to indicate how lacking in "teeth" was the Federal drug law at that time, the only criminal legal action available to the Government against the manufacturer, was that of a label misbranding charge. The product was labeled an "Elixir," that is, a hydro-alcoholic medicinal, which is fact it was not.

Shortly after this 1937 incident, as some of you will recall, there was again, as a result of the "Public's expectations of medications," a tightening of the act that in effect, required "safety" of use. But note, even then, no sense of urgency was felt for a mandatory requirement of "effectiveness for the purpose intended." Finally in our rundown of FDA history, let it be noted with the impact of the Kefauver hearings and the tragedies of the thalidomide disaster and its phocomelias, we moved forward with legislation that included an effectiveness requirement for the marketing of medications - I refer to the Harris-Kefauver Amendments of 1962.

At this point, I often ask myself - who among us had given serious thought to the teratogenic effects of medications prior to 1962? As to German measles, yes; but as to medications, few, I'm sure. Today, in 1967, such considerations are of prime concern to all prescribers, especially where there is a possibility of the patient being in the first trimester of pregnacy. Yet, if we had had an observant Flemming of penicillin fame in our midst, and if he had happened to thumb through the annual publications in the veterinary field, he might have noted back in 1959 or 1960, a report that pregnant sheep pastured in early fall, on certain meadow ranges in Idaho, give birth to deformed lambs. Why? A plant, a species of veratrum (Veratrum Californicum) carries at that time of the year a sufficient percentage of the offending glycoside or alkaloid to cause the phocomelias - and this is a drug we use in eclampsia, is it not? The signs were around us and we saw them not.

So much for our look at history. It does indicate the pressure of public opinion--slow, to be sure, but effective--of demanding sufficient governmental controls over medications to make them not only "safe," but "effective." As scientists, you know that absolute safety can never be guaranteed but reasonable legal safeguards can be and are being implemented by scientists such as yourselves, serving as "opinion molders" as to the needs in this area.

I interject at this point a bit of history and current events as to your specialty, radiopharmacueticals, and here I surely bring "Coals to Newcastle."

From writings of such knowledgeable individuals as Frances Kelsey and Earl Meyers of FDA, pharmacist Briner of NIH, Margaret Glos of Nucleonics, Merrill Bender of Roswell Park, Richard Cunningham, of AEC, and other of you, I note a sense of urgency on your part to work more closely with Government on regulatory matters, particularly in the area of clinical use of radiopharmaceuticals or medications. Again, I repeat, this is "opinion molding" and of the finest type. This interest of yours is especially significant, in view of the fact that nuclear medications in 1966, according to Glos, was on an $8 to $10 million volume and radiochemicals, another $6 to $8 million business.

As I understand the current status of radiopharmaceuticals of investigational nature, the U.S. Atomic Energy Commission currently regulates the medical use of byproduct materials by licensing the manufacturer and clinician user. Also, radiopharmaceuticals, since 1962, have been exempt from the Food and Drug Administration's investigational drug laws and regulations by order of the Commissioner, an exemption necessitated to date by FDA's lack of competent manpower to act in this area.

I suspect also from my cursory review of your specialty area, that the AEC regulations permit manufacturers of radiopharmaceuticals to market in interstate commerce products that are in investigational status or clinical trials, an exemption not normally allowed by FDA or PHS(as to biologicals) for investigational medications under their jurisdiction.

I gather also that this apparent exception to some, if not all clinical trial status radiopharmaceuticals, is a comforting one to those of you who are fearful that on the termination of the present exemption privilege, currently used radiopharmaceuticals may be ordered by FDA from the market place until approved NDA's are obtained. Dr. Earl Meyers, Director of the Division of Oncology and Radiopharmaceuticals, has indicated that NDA's for radiopharmaceuticals now in routine use, should not take long in processing.

Goldstein, in his article, "FDA and Radiopharmaceuticals: Waiting for the other Shoe to Drop," states: "Assuming, as almost everyone does, that FDA control will be more rigorous--and certainly more restrictive as far as investigational drugs are concerned--why is everyone eager to have it assume jurisdiction? A veteran clinical investigator sees it this way. The responsible manufacturers--and believe me, the Abbotts and Squibbs have a lot of reputation riding on radiopharmaceuticals--would like FDA to step in before there is a major catastrophe. Regulations after an accident are always punitive. I'd say that radiopharmaceuticals have been handled better and more safely than most other types of drugs, but there's always the chance of a nasty accident, which might not have anything to do with radioactivity."

On the opposite side of the polemics here, Goldstein points out, "A more cynical view comes from a marketing executive: - 'The big producers are most eager for FDA control because they figure the high cost of clinical investigations will drive the small competitors to the wall. They just can't afford to spend $100,000 on an NDA'(New Drug Application, not now required of reactor-produced radionuclides)."

"That's very true," replies a small manufacturer, but he wonders, "Is Abbott, whose radiopharmaceutical business adds up to a pretty small part of total sales--maybe $14 million--any more willing to spend $100,000 to push through a limited-volume drug than the small guy"--and the debate rages on.

The question quite likely is a moot one, for as I understand it, the public's expectation as to medications--safety, effectiveness, and all necessary "watch dog" monitoring--has already been met by Congress and merely awaits full implementation; and such implementation covers not only the safety and effectiveness of the products as radiopharmaceuticals per se, but also as effective medications per se, medications properly formulated as to micro particle size of medicament, percentage strength, excipient, diluent, vehicle, process of fabrication including sterility and pyrogen testing, and other important factors that pertain to therapeutic effectiveness such as minimal side effects, and established contraindications, that is, the "adem" of a medication per se--its absorption, distribution, elimination, and metabolism.

I base my statement on the possibility of the mootness of the issue on such statements as made by Bryant Jones, M.D., of the Bureau of Medicine, FDA--a statement included in a presentation made at the U.S. Naval Medical School at Bethesda, in May of this year--when he stated, "The exemption to the 'Exemption of New Drugs for Investigational Use' applies only to the investigational use of radiopharmaceuticals, and in particular only to those that are reactor produced." "In the memorandum of understanding," he stated, "between FDA and AEC only radiopharmaceuticals that are reactor produced are exempt from FDA investigational use requirements. Cyclotron or linear accelerator produced radioactive nuclides are not exempt from the provisions of the New Drug Regulations."

In concluding this phase of tonight's discussion, I suspect I have reminded you, that you too are "a public," and that your opinions, expectations, and demands regarding controls on radiopharmaceuticals are sought and needed by this Nation, and that such opinions and recommendations will eventually be reviewed by that greater public, the American public, in the press and yes, too, in the courtrooms of the Nation, should accidents of alleged negligence occur. I repeat once again--you are indeed "opinion molders" in an important phase of modern day American medicine.

I could move on now and discuss in detail with you the FDA act and regulations as they relate to investigational drugs. However, I note this material has appeared in your literature many times so we'll dispense with a discussion of Forms FD 1571, FD 1572, and FD 1573 and the regulations involving Phase I, II, and II of investigatory drugs.

Let it suffice for us tonight, in this connection, to point out a few practical points in connection with investigational activities that should be observed or noted in any sound legal and ethical quality control program. These are points that assure the public of its expectations as to safety and that are also designed to help protect the investigator.

1. Where one is involved in a study under Phase III (clinical testing) and reporting to a principal investigator, he has an obligation to himself to determine the principal investigator's reputation for quality controls. Is it possible for other of his investigators (physicians) to submit "graphite" reports on deceased or nonexistent patients? To not check on this point leaves one in a position of embarrassment should the names of all clinical investigators working with the principal investigator be released at the time of the exposé.

2. Incidently, many drug firms since the Boston exposé have tightened up on their quality control testing programs, and can quickly spot situations where there are more patient reports than are possible under the agreed upon protocol study filed with FDA.

3. The written consent from the fully informed patient or volunteer is another matter that needs coverage. Dr. Saenger spoke of his concern on this issue this morning. The final Federal word on the subject evidently has now appeared in the *Federal Register* of June 20, 1967. In brief, written consent is required *in all* cases of volunteers (not patients) and for patients (those under treatment) unless the clinician in his professional judgment deems this not feasible or contrary to the best interest of the patient. Note that *no* exception to the consent rule is permitted as to volunteer subjects. "Not feasible" has now been defined as "cases where the investigator is not capable of obtaining consent because of an inability to communicate with the patient or his representative;" for example, "the patient is in a coma or is otherwise incapable of giving consent, his representative cannot be reached and it is imperative to administer the drug without delay." As an aside, we recommend that when consent is obtained, the physician record not only the date but also the time for obvious reasons should litigation ensue and the patient claim "under sedation" at time of signing the consent form. Also where the physician elects not to obtain consent, this fact should also be recorded on the patient's chart at the time such a decision is made and the reason why.

It is to be noted that the June 20 regulations have dropped the term "informed" from the newly revised FDA patient consent policy but the description of the information which the clinician should give a person when consent is sought remains in the regulation. This information includes the nature, expected duration, and purpose of administering the medication, the methods and means of administration, hazards involved, existence of alternative forms of therapy, if any, and health benefits that might result from the use of the drug.

4. The American Medical Association Law Department, in 1961, published, "Medico-legal Forms with Legal Analysis," a brochure I highly recommend to clinical investigators. Form 29, page 37 deals with consent relative to investigational drugs.

5. Finally, let us not forget that out of the Nuremberg trials involving human experimentation (15 defendants were found guilty, 7 were hanged, 4 were physicians) came several codes of conduct that one should be cognizant of. I refer to the Helsinki Declaration adopted by the World Medical Association, the PHS-NIH, and U.S. Army requirements relative to Investigational drug tests, the Statement of Principles on the Use of Investigational Drugs as approved by the Board of Trustees of the American Hospital Association and the American Society of Hospital Pharmacists (1957), and the American Medical Association's recent Ethical Guidelines for Investigations."

We have now reached that point in this discussion of the public's expectations regarding pharmaceuticals where we should take a look as to what the public does in individual cases, when his expectations as to safety and efficiency are not met--and here of course we refer to his legal recourse in the field of tort negligence or malpractice.

Let me point out, and this is most important, that laws, statutes, regulations, standards, and codes of conduct as just discussed, as well as policy and procedural manuals of departments and institutions, all designed to improve and protect patient care, become, in time, tools to be used by prosecutors, courts, and attorneys in determining the degree or standard of care below which one might conceivably be found guilty of criminal or tort negligence, or in violation of codes and statutes or "good practice" norms. I shall mention two specific cases to illustrate the point.

You may recall that the Board of 15 Regents of N.Y. State, in a unanimous decision, ruled a few years ago that the two doctors from Sloan Kettering Institute for Cancer Research who conducted the cancer cell studies at the Jewish Chronic Disease Hospital, have their medical license suspended (but stayed execution of sentence, placing the physicians on probation for 1 year) for fraud and deceit in the practice of medicine. They were charged with not informing the patients of the true nature of the study and with failure to obtain the voluntary consent of the fully informed patient.

My second illustration indicates specifically how the individual, "as a public," insures redress when he feels that the safety and efficacy of medications have been bandied about in his own case.

He goes to court and seeks satisfaction usually in a tort malpractice action. In such a case, the plaintiff must prove but three points:

(1) there was a legal duty for the defendant to exercise care,
(2) such duty was not exercised, and
(3) as a result, he, the plaintiff was injured.

The defendent, in responding to the suit, has several legal defenses available to him, such as:

(1) He did use proper care.

(2) He proves contributory negligence on the part of the plaintiff; but let it be noted here that reliance by the plaintiff on the knowledge and skill of the clinician is not considered "contributory negligence."

(3) In situations involving items not inherently dangerous, he may be able to prove that his negligent act was not a direct or proximate cause of the injury. However, this defense is not

available in medication cases for such medications are "items inherently dangerous." (Thomas vs. Winchester 6 N.Y. 397 (1852.)

It is difficult to understand how a defendant who has not followed all Federal rules and regulations and codes of conduct of national associations and the like, such as hospital and medical staff regulations and bylaws, can escape negligence charges in cases involving clinical trials.

In fact, a recent case in Illinois has medical and hospital authorities quite concerned over the extension of this responsibility doctrine as it applies to physicians and is carried over to the institution in which the injury occurs.

The case in question is Darling vs. Charleston Community Memorial Hospital, 211 N.E. 2nd 253 (Ill.) November 18, 1965. The facts of the case run about as follows: A young man was brought into the emergency room of the hospital. While playing football he had broken his leg. His family physician had been called, and he, with the assistance of hospital personnel, set the leg. The patient later complained of great pain. The doctor did not see the patient but did order sedation.

It was proved that the cast had been improperly applied. Action was brought to recover damages for alleged negligent medical and hospital care which resulted in the amputation of the right leg below the knee. The physician made a $40,000 settlement out of court. The hospital decided to try the case on the grounds, among others, that it did not practice medicine. The hospital had a verdict of $150,000 rendered against it. The case concerned itself with the legal effect to be given to evidence concerning the standard of care and diligence and the legal effect to be given to hospital regulations adopted by the State Department of Public Health under the Hospital Licensing Act, to the Standards for Hospital Accreditation by the Joint Commission and the bylaws of the hospital. Among other highlights in the court's decision was that the Standards for Hospital Accreditation, the State licensing regulations and the defendant's own bylaws demonstrated that the medical profession and other responsible authorities regard it as both desirable and feasible that a hospital assume certain responsibilities for the care of the patient. The court then pointed out that the hospital did not live up to these standards: that it failed to have a sufficient number of trained nurses for the bedside care of all patients at all times capable of recognizing the progressive gangrenous condition of the plaintiff's leg and of bringing the same to the attention of the hospital administration and to the medical staff, so that adequate consultation could have been secured and such conditions rectified. Also, the hospital failed to require consultation with or examination by members of the hospital's surgical staff skilled in such treatment, or to review the treatment rendered. . .

The point of the case applicable to this discussion tonight is simply that the hospital's own bylaws, the State licensing regulations, and joint commission standards were found not to have been complied with, and such findings were allowed into the courtroom to bolster the negligence charge.

I ask that we apply this type of thinking to the "public's expectation regarding pharmaceuticals" and then consider the plight of the investigator in court on a tort negligence charge as the plaintiff's attorney, using FDA and other regulations, Codes of Conduct such as those endorsed by the American Medical Association and the American Hospital Association as to investigational drugs, or Codes of Conduct or action that you, as opinion molders and experts, develop here or elsewhere, drive home to the judge and jury, noncompliance with these safeguards. The "public's expectations" regarding pharmaceuticals, be they radioactive or nonradioactive, does indeed become a very real one to that investigator at that time. We can only hope that he carries ample malpractice insurance.

I have attempted this evening to depict for you the public's expectation relative to pharmaceuticals, and in particular those medications not cleared by FDA for sale in interstate commerce; that is, investigational drugs.

I trust I have given to you the same sense of concern that we as attorneys have in this matter, as it relates to those practicing in institutional settings and to the facilities themselves.

THIRD GENERAL SESSION

SUGGESTED DISCUSSION QUESTIONS FOR WORKSHOP

1. How do radiation exposure and patient safety (degree of morbidity) in nuclear medicine procedures compare with similar diagnostic X-ray procedures?

2. What can be done now to reduce the radiation exposure to patients and still maintain diagnostic benefit from nuclear medicine procedures?

3. What can be done now to reduce the radiation exposure to personnel other than patients (physicians, technologists, and so forth)?

4. How great an internal radiation dose should be permitted in the case of individuals exposed as subjects in research studies?

5. To what extent will diagnostic screening tests, using radiopharmaceuticals, become an integral part of medical practice?

6. What will it take to provide adequate numbers of appropriately qualified nuclear medicine physicians and technologists? Who should establish these qualifications?

7. What are the possible approaches for facilitating elimination of radionuclides from the body upon termination of their use for diagnostic procedures?

8. Are short-lived radionuclides really the answer to dose reduction?

9. Are the present-day radionuclide standards reliable to insure accurate calibration of instrumentation?

10. What impact will accelerator-produced radionuclides have upon nuclear medicine in terms of new clinical applications and exposure to the general population? What is the necessity for these radionuclides being readily available?

WORK GROUP I REPORT

James L. Quinn, III, M.D.[1]
Henry N. Wellman, M.D.[2]

We decided that this report should express the concensus of the group, and we directed ourselves to four areas rather than the individual questions, knowing that these various areas covered several of the questions, mainly on patient exposure, personnel exposure, radiopharmaceutical production, training and manpower.

First, the patient exposure. The concensus of the group was that the current radiation dose to target and critical organs in generally accepted nuclear medicine diagnostic procedures was not excessive, and in general was equal to or less than the comparably informative roentgen examination. In addition to this, the associated morbidity and mortality risk of the nuclear medicine diagnostic procedure was far less.

However, despite the fact that the patient or organ doses do not seem excessive, dose reduction is desirable when reasonable, but not at the expense of optimal information recording.

Despite the fact that there has been no obvious deleterious effect from these nuclear medicine procedures, this does not preclude the possibility of unrecognized subcellular damage. Accordingly, investigations to this point should be undertaken with the support of regulatory agencies and other interested groups. In addition to this, the possible differences in radiation effect on subcellular structures as a result of dose rate deposition for the same cumulative dose demands elucidation.

The plea was made for more and better biological turnover data with which to calculate accurately the internal organ dosimetry from administered radiopharmaceuticals.

With regard to personnel exposure, the advent of radionuclide generator systems has created new problems in nuclear medicine personnel protection. It was noted that exposure levels of personnel has risen in both hospital and radiopharmaceutical industry laboratories. Although still well within acceptable limits, this exposure is rising relative to personnel in X-ray facilities.

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In addition, reports are increasing of facility contamination as well as internal contamination of personnel. The correction of these problems, once recognized, can be at the local level.

It was felt that the use of film badges alone for personnel monitoring was not adequate and that additional detection systems for recognizing acute exposures was desirable. Periodic *in vivo* or bioassay monitoring of personnel is recommended to assess internal contamination levels.

With regard to radiopharmaceutical production, as the use of short-lived radionuclides increases, it is expected that end stage preparation prior to administration will take place locally, relying upon component and system rather than final product testing. Emphasis on adequate system and component testing will serve to make short-lived radiopharmaceuticals available to the patient while still assuring necessary product quality control. It is expected that nuclear medicine will continue to have the close cooperation with industry in the development of newer radiopharmaceuticals, perhaps even in joint physical facilities.

As to training and manpower, there was unanimous agreement that a shortage of trained technical personnel is an acute problem facing the field of nuclear medicine today. This has resulted in part from a failure of the field of nuclear medicine to provide adequate numbers of personnel trained in depth, plus an undue delay on the part of interested professional societies to agree and to act on remedial solutions.

Financial support of training programs by appropriate government agencies cannot be expected until the specific questions of *who*, *what*, *how*, and *how many* need to be trained are answered. It was felt that this meeting should adopt a resolution to the effect that the involved and interested parties act as quickly as possible to resolve this seeming impasse, and that a study is needed to document the manpower needs in the field of nuclear medicine. It is therefore proposed that the Society of Nuclear Medicine be asked to undertake such a poll as soon as is practicable.

WORK GROUP II REPORT

William H. Briner[1]
Paul Numerof, Sc.D.[2]

Being the naive lambs that we are, our group very dutifully followed the list of suggested discussion questions for our workshop, and we will proceed with our report based upon these questions

1. How do radiation exposure and patient safety in nuclear medicine procedures compare with similar diagnostic X-ray procedures?

The group consensus is that nuclear medicine procedures in general give patients absorbed doses lower than those in similar diagnostic X-ray procedures. For example, a GI series plus gall bladder and IVP studies give X-ray absorbed doses in excess of those experienced in many isotope series. A GI series may easily give in excess of 20 rads per study.

Another aspect to be considered is the morbidity and the mortality of the respective procedures. In IVP, a morbidity rate of one per thousand and a mortality rate of one per one hundred thousand has been reported. These are substantially in excess of nuclear medicine rates.

Also to be considered is the fact that some clinical nuclear medicine procedures give information more quickly than is obtainable by standard X-ray procedures. An example is bone scans with a dose of approximately 2 to 4 rad, compared to something in excess of 1 rad per X-ray exposure for a skeletal X-ray survey. However, bone scanning often indicates the presence of lesions earlier than X-ray skeletal surveys, and often outlines a greater area of involvement than is seen on a conventional X-ray.

It was stated that there are fewer repeat examinations required in a well-managed nuclear medicine department than is the case in the average diagnostic X-ray department in a hospital. In the latter case there may be as many as 10 percent repeat examinations required because of technically inadequate examinations.

It was the considered opinion of this group that very few diagnostic X-ray procedures can be replaced by nuclear medicine procedures at this point in time. Usually these procedures are complementary; exceptions to this opinion would include placentography and bone scans.

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2. What can be done now to reduce the radiation exposure to patients and still maintain diagnostic benefit from nuclear medicine procedures?

Reduction in radiation exposure to patients can be achieved by three methods: (1) better and more sensitive isotope detectors and instrumentation; (2) adjustment of administered radionuclides to patient requirements, more organ-specific radiopharmaceuticals; (3) reliance on the nuclear medicine physician as a consultant rather than a purveyor of services.

Also to be considered is the use of lower administered activities with prolonged periods of observation in static studies.

3. What can be done now to reduce the radiation exposure to personnel other than patients, such as physicians, technologists, and so forth?

The problem of radioisotope workers may be that of material ingested as a consequence of poor laboratory work habits rather than an external exposure. However, in general external exposures of nuclear medicine personnel are below that of diagnostic X-ray personnel.

The use of larger activities of short-lived radioactive nuclides may result in higher radiation dose to the hands. Furthermore, short-lived isotopes may be conducive to a lowering of health physics standards because of the limited period of contamination.

To reduce the risks of unsuspected internal contamination with volatile isotopes, laboratories should consider making measurements on their personnel, such as thyroid counts on those working with large amounts of ^{131}I. Other bioassay techniques may be equally valuable in other situations.

4. How great an internal radiation dose should be permitted in the case of individuals exposed as subjects in research studies?

In general, the feeling of the group concerning this matter indicated a maximum upper limit similar to that imposed upon the occupationally exposed individual. With regard to pregnant women and children, considered judgment of a responsible physician must always apply. The group felt that no firm recommendations could be made regarding children and pregnancy, and that this judgment would best be left to the clinician involved.

In addition, it was considered mandatory that informed consent be obtained in normal subjects participating in such studies.

One method that has proved effective has been the selection of patients undergoing radiation therapy for known life-threatening malignant conditions. In such patients the additional radiation dose from a nuclear medicine procedure is in most cases insignificant to that being delivered by the conventional radiation therapy procedure.

5. To what extent will diagnostic screening tests, using radiopharmaceuticals, become an integral part of medical practice?

To provide a working definition on screening tests, the following was adopted: Screening tests are those for which there is no immediate clinical indication to justify the procedure.

It was the group's opinion that based on this definition screening tests with radiopharmaceuticals are not likely to become routine within the present state of the art. Abuse of nuclear medicine procedures will be avoided when good professional judgment is exercised by the clinician directing a nuclear medicine unit.

However, in a consideration of selection of a procedure, it is likely that nuclear medicine would be the preferred choice because of the lower morbidity and mortality associated with nuclear medicine methodology.

6. What will it take to provide adequate numbers of appropriately qualified nuclear medicine physicians and technologists? Who should establish these qualifications?

The body of opinion of this group indicates that there will be an acute shortage of adequately trained physicians and technologists in this field until such time as board certification of nuclear medicine as a specialty or subspecialty occurs. It is strongly suggested that a firm recommendation in this direction be stated in the proceedings of this symposium.

As a recognized specialty, nuclear medicine would also tend to attract additional practitioners from the ranks of medical students and interns. When there is an adequate supply of properly trained and recognized physicians in this field, in the consensus of the group the feeling was that the training of technologists will surely soon follow.

7. What are the possible approaches for facilitating elimination of radionuclides from the body upon termination of their use for diagnostic procedures?

Three possible isolated approaches were described: (1) the use of stable iodide in an exchange reaction with thyroid-bound I-131; (2) the use of alginates administered to patients receiving radioactive strontium; (3) laxatives for patients receiving radiopharmaceuticals preferentially excreted by the GI tract.

However, it is recognized that prolonged administration of laxatives may produce the problems of patient dependence and acceptability, as well as the additional burden of such procedures on already overworked hospital personnel.

It was the consensus that this is a field in which additional effort is needed. For example, much past research directed toward reducing body burdens of heavy metals was undertaken with the thought of removing macroamounts of these compounds from their site of localization. It is seldom indeed that such relatively large amounts of these materials would ever be localized in the body as a result of a nuclear medicine procedure. Thus it may be possible to achieve some degree of success in areas involved in past failures.

8. Are short-lived radionuclides really the answer to dose reduction?

It was the consensus that short-lived isotopes are not necessarily the total answer to dose reduction.

Several clinical members expressed the need, as shown by their own experience, for more than one agent, regardless of the physical half-life of the isotope employed.

It was agreed that additional research should be directed toward the development of radiopharmaceuticals with shorter effective half-life rather than concentrating on physical half-life alone.

It was also considered important that attention be directed to the time-dose relationship of the radioactive agents employed in nuclear medicine.

In this context the following question needs to be resolved: "Which poses the greater hazard, a somewhat smaller integrated absorbed dose from a short-lived radionuclide delivered over a short period of time, or a somewhat larger integrated absorbed dose for a longer-lived isotope but delivered over a longer period of time?"

Finally, acknowledgment of certain other potential hazards in the use of short-lived nuclides must be made. The physical advantages of a short-lived isotope could be negated by a formulation misadventure on the part of inadequately trained and supervised personnel.

9. Are the present day radionuclide standards reliable to insure accurate calibration of instrumentation?

The scope of reference sources currently available is not considered satisfactory. It is essential that reliable radionuclide standards be made available to insure accurate instrument calibration.

10. What impact will accelerator-produced radionuclides have upon nuclear medicine in terms of new clinical applications and exposure to the general population? What is the necessity for these radionuclides being readily available?

The group felt quite simply that there is at present time insufficient information available to make judgment on that matter.

WORK GROUP III REPORT

Thomas G. Mitchell, Ph.D.[1]
Donald W. Brown, M.D.[2]

Is it necessary to reduce radiation dosage? Yes. Accumulated evidence supports the single hit theory; thus, all unnecessary radiation should be avoided. This is our recommendation even though radiation doses administered in presently utilized clinical isotope procedures are far below those which have been observed to be teratogenic or to cause mutations.

What constitutes a harmful or "bad" dose of radiation cannot be clearly defined at present. Research efforts designed to delineate this should be supported vigorously. In general, anticipated harmful effects can be divided into genetic and somatic areas. In man it is believed the acute mutation doubling dose is 50 rads and the chronic mutation doubling dose is 100 rads. In humans the teratogenic dose is not defined, but a dose over 100 rads to the target organ should be avoided (except for therapy). Some effects attributable to excessive radiation may be leukemia, thyroid neoplasm, lung carcinoma, life shortening, and developmental abnormalities.

The general problem of radiation exposure to normal volunteers was thought to be best considered on an individual basis. No member of the group was willing to propose any particular radiation dose as acceptable for volunteers. The potential risk to the patient, the compound to which the radionuclide is labeled, the age, and general patient conditions are all variables which would preclude making any judgment on this.

Many methods of reducing radiation dosage in nuclear medicine were discussed. We all agreed that the most important single method of achieving this was by having an intelligent, highly motivated and well-trained physician responsible for the administration of the nuclear medicine area. In many instances appropriate screening by this physician could reduce the number of procedures carried out by as much as 50 percent. Too many unnecessary and perhaps useless procedures have characterized some of the recent practices in this field. This is primarily a physician education problem, but also, in part, a licensing and/or regulatory problem. The answer, in part, lies in the increasing funds available for training men schooled in nuclear medicine.

The four broad areas of investigation which may lead to reducing radiation exposure in nuclear medicine are: instrumentation;

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(2) development of new radiopharmaceuticals; (3) increased use of stable isotopes; and (4) activation analysis.

While it is likely that radiation dose reductions by a factor of a thousand can be achieved by the introduction of new radiopharmaceuticals, for example, the recent introduction of ^{123}I in place of ^{131}I, it is expected that reductions of only a factor of ten can be achieved by better instrumentation.

There is no excuse for the performance of diagnostic studies with antiquated, relatively insensitive equipment. Patient radiation exposure should be minimized by using the most sensitive and reliable instruments currently available to the profession for these purposes.

Presently available commercial equipment is adequate in most cases to do the job for which intended. However, the use of the equipment is not always in keeping with sound physical principles and it is recommended that standard procedures for daily calibration of instruments be formulated. This should include procedures for energy calibration in the case of spectrometers and count rate-density calibrations for photoscanning devices.

It was recommended that standards of instrument performance be formulated and that manufacturers provide information on performance specifications of their instruments, to include, as a minimum, the spectral distribution of noise from photomultiplier tubes and energy resolution of the crystals.

In the field of improved radiopharmaceuticals it was felt that more intense efforts should be made to shorten biological half-lives. One way of achieving this is to utilize stable agents which block the metabolism of the radioactive compound or bind it in such a manner as to hasten its excretion. Examples are the use of iodides and thyroid blocking agents for ^{99m}Tc and iodine isotopes, and injection of stable mercury hopefully to reduce renal tubular binding of radioactive chlormerodrin. Occasionally, careful study will reveal a slightly different pharmaceutical form of an isotope which will accomplish the same testing purposes but result in a shortened biological half-life; for example, substituting ^{131}I cholograffin for ^{131}I albumin in cardiac scanning.

We were in agreement that in general the use of short half-lived isotopes was desirable and therefore the development and use of generators should be supported. In this light, three practical suggestions were made: (1) that the pharmaceutical companies be encouraged to make sterile, pyrogen-free "kits" suitable for concocting compounds such as technetium-labeled sulfur colloids and albumin in nuclear medicine laboratories; (2) it was felt that the Society of Nuclear Medicine should be asked to form an *ad hoc* committee to establish uniform standards for pyrogen, sterility, and other necessary quality control procedures, to assure the use of generators and modified generator eluants in a safe and efficacious manner on a day-to-day basis in the nuclear medicine laboratory; (3) decentralization of pharmaceutical companies with the development of "milk delivery" type operations should also be encouraged.

Accelerator-produced radionuclides can offer radiation properties that reduce radiation exposure and dose and for that reason may become more important in the future. The group felt that federal funds are needed to support a number of medical cyclotrons throughout the country to establish a means of developing new uses of cyclotron-produced radionuclides and labeled compounds.

One member noted that presently available "medical" cyclotrons are limited to low outputs and would not be suitable as producers for large-scale routine clinical uses. They, however, could be valuable in new developments of radiopharmaceuticals affording reductions of absorbed radiation dose. The group agreed that the AEC should be urged to make more easily available the high-output 86-inch cyclotron at ORNL. The large-scale production capability of this machine and available target technology at ORNL are of the order needed for routine uses. The increased use of any other large-output AEC cyclotron, particularly near large airports, should also be encouraged.

Ways of reducing exposure to technicians working in nuclear medicine were also discussed. It is felt that nearly all of the significant exposure presently comes from handling the preparations rather than from patients carrying isotope burdens. Lead glass windows and keeping the syringe in a lead boat whenever possible were suggested. Also, technicians should rotate the duties of "milking" generators. The use of a whole-body counter for monitoring technicians on a routine basis has been found helpful and was also encouraged. An aside on technicians was that it was felt that the NCRH should strive to achieve coordination of the various groups concerned to obtain uniform accreditation of technicians in order to be recognized by the AMA Council on Accreditation and end the confusion rampant in this area at present.

There was a great deal of discussion about what should be on the package inserts soon to be requested by the FDA on radiopharmaceuticals. The group felt emphatically that this should not give pregnancy and age under 18 as absolute contraindications, but only as relative deterrents depending on the clinician's judgment in the particular case. It was also recommended that details of decay, with percentage and energy of radiation emitted, should also be provided. Perhaps photon energy spectrum information would also help. In this regard it was hoped that the FDA could obtain a larger staff to include experts in nuclear medicine, radiopharmacology, radiophysics, and radiation biology, and it was also felt that close cooperation between this staff and the leaders in nuclear medicine should be encouraged.

Our group concludes that the proper use of nuclear medicine instrumentation in the hands of qualified technicians, plus the elimination of unwarranted diagnostic procedures, as dictated by the nuclear medicine physician, are areas of concern that demand our attention. Attention to these areas can reduce the radiation exposure to patients while still maintaining diagnostic benefits.

WORK GROUP IV REPORT

E. Richard King, M.D.[1]
David E. Kuhl, M.D.[2]

The prudent use of radiopharmaceuticals in medical diagnosis is based on primary consideration for the patient's welfare. For each procedure the physician balances the probability of adverse effect against the probability of benefit to his patient. Radiation dose is the important potential hazard. Characteristically, radioisotope studies involve very small amounts of material, and reactions from chemical toxicity are rare. This radiation dose depends on the physical properties of the radionuclide, the biologic properties of the compound, the distribution of the compound, and how much radiopharmaceutical must be given to obtain a required statistical accuracy of data with the detection equipment available. An optimum choice of radiopharmaceutical, instrument, and technique should give a maximum ratio of useful information to radiation exposure. How well these choices are made determines the benefit to the patient, even though it is not yet completely clear how these choices can best be made. There is no recognized standard of tissue tolerance dose in clinical nuclear medicine.

The recommendations below are intended to encourage the developement of nuclear medicine to produce even more patient benefits by:

(1) Assuring the availability of physicians and supporting personnel who have special competence in nuclear medicine and associated sciences;

(2) Increasing knowledge of the magnitude of potential adverse effect associated with each test;

(3) Encouraging use of more efficient detection instruments; and

(4) Increasing the use of radiopharmaceuticals with more optimum physical properties; that is, those with a high ratio of information yield to radiation dose.

Recommendation I. Dose Effect Studies. Recognizing that the basic consideration of the conference was a discussion of possible methods of radiation dose reduction, and recognizing that such considerations would likely involve the substitution of short-lived radionuclides for longer-lived radionuclides used for the same

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clinical test, and that such substitution would allow higher activities of short-lived radionuclides to be used, our panel recommends that:

(1) Certain radiation biologic principles be applied to investigative studies comparing the dose effect of comparable short half-lived and long half-lived radionuclides; that is, ^{125}I, and ^{131}I, ^{87m}Sr and ^{85}Sr, ^{197}Hg and ^{203}Hg.

(2) Such studies could include a comparison of the dose effect as judged by the time-dose relationship, in lethality studies of total body irradiation of small animals and comparison studies of specific selected target organs; for example, the kidney, thyroid, bone marrow, and so forth.

(3) Studies of the significance of the shoulder portion of the typical cell-survival curves; for example, whether this shoulder obviates detrimental effects owing to the low absorbed dose of radiation as delivered by diagnostic levels of radionuclides.

(4) Studies of the cell cycle and DNA replication for various normal tissues and the effect of low absorbed doses of radiation as delivered by diagnostic levels of radionuclides.

(5) Studies of the effect of the oxygen enhancement ratio insofar as the possibility of oxygen tension altering the radiosensitivity of certain tissues to the dose effect of the absorbed dose as delivered by radionuclides.

(6) Studies of the effects of the distribution of radioisotopes at the suborgan level upon the organ dosimetry. Examples of this problem, the irregular localization of iodine in the colloid of the thyroid follicles, the irregular uptake of mercurials in the renal cortex.

(7) The panel further recommends that consideration be given to the formation of a group, composed of qualified individuals from several institutions, to develop protocols on the above studies as part of a national cooperative program.

Recommendation II: Efficacy. The experiences of 30 years of the use of radionuclides in medical diagnosis with the absence of significant adverse effects have amply demonstrated the safety of such studies as customarily performed, and the acceptability of the radiation exposures resulting from these procedures. In the interest of the continuing development and improvement of this expanding field of nuclear medicine, this panel suggests the following principles. Although adverse effects from radiation exposure from the traditional diagnostic uses of radionuclides have not been demonstrated, it is desirable that radiation effects from such procedures be reduced as much as is compatible with the obtaining of the desired medical information. To this end we recommend:

(1) Recognition that the evaluation of efficacy is a difficult problem for which objective guidelines need to be developed.

(2) That diagnostic procedures, employing radioactive materials, be performed only when clinically useful diagnostic information can be expected.

(3) That the radioactive substance employed for such studies be selected to provide the least radiation effect compatible with the desired goals of the study; for example, the possible substitution of ^{57}Co for ^{60}Co labeled cyanocobalamine.

(4) That wherever possible more efficient detection equipment be used so as to provide the information desired with the lowest radiation dose possible compatible with these desired goals.

Recommendation III: Qualifications of Physicians. Recognizing the rapid expansion of the practice of nuclear medicine, the widening demands for professional competency in the field, and the importance of such competence in reducing the radiation exposure to the population from nuclear medicine procedures, and recognizing that government agencies, hospitals, and the American public traditionally have looked to the medical profession to indicate through professional certifying bodies those members of the medical profession with special qualifications to practice in certain specialized areas of medicine, it is the opinion of the panel that a group of recognized authorities be constituted to define the qualifications desirable for those physicians who will practice nuclear medicine, and to assure certification of competence in the field.

Recommendation IV: Qualifications of Allied Professional Personnel. In the interest of continuance of the orderly advancement of the field of nuclear medicine, and recognizing the contributions of the nonmedical professional individuals in this rapidly expanding field, it is the opinion of this panel that a group of recognized authorities should be constituted to define the qualifications desirable for those individuals (physicists, chemists, engineers, pharmacists, and others) who will serve the field of nuclear medicine in these capacities and to assure certification of competence in the field.

Recommendation V: Technical Personnel. Recognizing the urgent need for increasing the supply of persons adequately trained to serve as technical personnel in nuclear medicine and the potential advantages of employment in this field, it is recommended that:

(1) A brochure describing the opportunity for careers in this field be prepared for distribution to secondary, junior college and college counselors, and students.

(2) Cooperation be encouraged between junior colleges, colleges, and clinical departments engaged in the practice of nuclear

medicine to develop cooperative endeavors and training programs. Such cooperative efforts might be coordinated by the local chapter of the Society of Nuclear Medicine.

Recommendation VI: Increase in Occupational Exposure. The panel wishes to state that it is aware of the possible increase in occupational radiation exposure that may result from the increased use of higher activities of short half-life radionuclides, and recommends that the entire group take cognizance of this as an area for further study.

DISCUSSION

Dr. Numerof:

I just wanted to ask Groups I and III for some clarification with respect to the elimination of any end product controls on pharmaceutical preparations. I'm not clear as to whether or not this is restricted solely to the use of intermediates of known quality and performance and elimination of final testing on that basis, or whether your group is suggesting, Dr. Quinn, that final product testing as a whole be eliminated. I would like to ask for some clarification on that before discussing it further.

Dr. Quinn:

In the present context of final product testing, Dr. Numerof, it was felt that it would not be possible to do final product testing prior to use, and that we may be having to do system or component testing prior to use, but the final product may be tested only in post hoc situation, not that final product testing, as such, should be eliminated. But with the current problems that we have, the new problems with these shorter-lived pharmaceuticals, this may be the only way in which we can provide these radiopharmaceuticals to patients for the accrued benefits, yet still protect the patient with the orthodox guidelines of safety of product manufacture.

Mr. Briner:

Let me ask you, Dr. Quinn: Is there inherent in this procedure some provision for a number of pilot batches to be formulated and subjected to comprehensive control testing to document the safety of the system before one actually gets into a clinical use situation?

Dr. Quinn:

Yes.

Dr. Maxfield:

This was a question that we discussed in our group also, and I think that what Dr. Quinn is suggesting is that we would like to see a kit developed for doing the pharmaceutical preparation of the short half-life isotopes. All of the components would be pretested before delivery to us and would be ready to be combined as needed. A similar case is the preparation of actinomycin-D, where we do not run routine tests on the components before reconstituting the compound for patient use.

Dr. Numerof:

While we are still on the subject of radioactive pharmaceuticals I would like to make a few comments concerning the statements in the report of Group III.

First, I feel that it is not the business of the Society of Nuclear Medicine to try to develop and to generate pharmaceutical standards concerning sterility, pyrogen testing and so forth. There is a duly constituted and authorized Federal body whose responsibility that is, and frankly I think the Society of Nuclear Medicine could direct its efforts in other directions since this is already well taken care of.

Secondly, I also question the specificity of the recommendation regarding decentralization of radiopharmaceutical manufacturers. In all seriousness, realizing that the problem exists, my preference would be that the radiopharmaceutical industry be encouraged to develop solutions to a problem which is known to exist, rather than making a recommendation as specific as this; for example:

With respect to generator-produced materials which have been more or less available since 1954, a solution regarding the pharmaceutical problems of sterility and pyrogenicity was developed, and these materials are now available from a large number of manufacturers. It would seem to me that this is the direction that the field should take, that the problems be delineated and described and then the solutions left to those who are most familiar with this area to develop solutions to the problem, rather than a group of this type giving specific recommendations without necessarily being aware of all the problems associated with the development of the solution itself.

Dr. Saenger:

Being a participant in the discussion of Group III, I don't think there was any intent to put the heat on the radiopharmaceutical industry, to which we feel a tremendous debt, but sometimes I think that there are those of us who feel that a few small prods in the direction of the radiopharmaceutical industry might work in the same way as the few small prods which occasionally are directed toward the medical profession when we feel that new services will be anticipated. I think this is generally recognized as a matter of adequate distribution, and the only point in this type of suggestion is that some of us who live in large metropolitan areas, but reasonably remote from airport facilities, find it rather difficult to be running a taxi service when we prefer to spend time with the patients. This may result in some increased inconvenience to the radiopharmaceutical manufacturer, but if the service is really worthwhile I think the patient would be ultimately willing to pay for it.

Dr. Hilberg:

I might say that, from what I heard, each group apparently accomplished the same thing that our group did, we insulted just about everyone in our group, with one exception, and it was bothersome because he was sort of chairing the meeting most of the way through, so we didn't get around to insulting the pharmacist. I don't know exactly why, but every time we started Briner stopped us.

Dr. Saenger:

I would like to insult him right now!

The only thing I took exception to in any of these panels was the definition of the screening test as defined by Group II, which left me a little unhappy, because I think the implication of saying that a screening test is a procedure that is really not necessary for clinical purposes kind of puts us in a position that we are standing out on the street corner with large nets trying to either trick or seduce people into the isotope labs so we can whomp them with some isotopes. In talking to most people, and knowing what we do in our place, we are not really looking for more work. We're trying to keep up with what is put to us. I think the definition of a screening test is one which is done at a simpler level in reference to the bodily insult suffered by the patient, and since I recently had some experience where my person was assaulted, I'm reasonably sensitive about these matters. In other words, I would presume that if one had the inside of his cranium investigated, it would be much easier to start off with an intravenous injection than with a whomping arteriogram. I think this is the type of screening that we have in mind.

Dr. Numerof:

I think we will have to leave Bill Briner's record unblemished because that definition wasn't his, it was mine.

We spent a good bit of time just arguing about what a screening test is, and we rapidly were getting no place. So, just for purposes of discussion we stuck to a definition (whether everyone agreed with the definition or not) and this is the definition we started with. We were exposed to other definitions, first order, second order, and so forth, of screening tests, and we figured it was a rapid means of making no progress at all. Whether one agreed with this definition of screening test or not, we just used this as a basis for argument--which we had in good measure.

Mr. Briner:

In further defense, and in deference to Dr. Saenger, I can only say that if he insists, Work Group II will now discuss this problem.

Dr. Hilberg:

Before you do, I may have helped with this definition a little bit, since I was part of Group II, and since I had received a request for such a screening test from a scientific group. We were to proceed with the scanning of thyroid glands in several hundreds of thousands of children, so this definition, I think, has some legitimacy to it--it can happen.

Dr. Brown:

I would like to clarify Group III's feeling about the first point raised by Dr. Numerof; that is, the setting of pharmaceutical standards by the Society of Nuclear Medicine. The intended context was not to assure the pharmaceutical manufacturer's part of it, but rather it would be very nice if there were a specific recommended set of procedures to follow in our own laboratories. For instance, when we make technetium sulfide how often should I get a batch and pyrogen test it or sterility test it?

Dr. Matson:

I think the point that has been struggled over here is whether there is a difference between good manufacturing practice in a manufacturing plant and good manufacturing practice in a hospital, for example. I think the basic principles as they have been evolved over a period of 30 years, since the American Pharmaceutical Manufacturers Association first took a crack at it, and up until most recently when the Food and Drug Administration has given very serious and detailed attention to this question--the basic principles that have evolved are universal principles. I think maybe what Dr. Brown was asking is: How can those basic principles be boiled down into a form that is easily understood by people who don't spend all their lives at the manufacturing end? To that extent I think it would be a very healthy thing to do.

Speaking of what Dr. Numerof was talking about here, I feel that the development of these things and the interaction of the manufacturers and investigators is a very natural one, and a lot of good things happen by experimenting along this line. Cooperation is a desirable thing. Thirty years ago a lot of hospitals thought they really should resist the commercialization of intravenous solution preparation, and should do it in the basement. I don't know whether there are any hospitals now that still try to do that, but it became obvious that the problems of maintaining good manufacturing practice in intravenous solutions were not simple, and it probably had to be done by an industry. I think the same thing will happen in cases where it is possible for manufacturing to decentralize, and in an industrial unit this will be the natural trend, so it doesn't worry me.

On the other hand, I don't mind cooperating with an investigator who has a 10-minute isotope if somehow we can help institute really good manufacturing processes in that investigation. We will both learn and develop mutual respect.

Dr. Jones:

My reason for entering into this debate is the fact that I was a participant in Group III in which this topic was discussed, and I think in some respects we may be off direction just a little bit. In defense of the formation of the committee under the aegis of the Society of Nuclear Medicine, I don't think we truly have to concern ourselves with the established procedures that are documented in the U.S. Pharmacopeia and the National Formulary, which contain accepted methods for sterility and pyrogenicity. But the present state of the art in nuclear medicine and radiopharmaceuticals is such that there is an enormous amount of investigation and pharmacy work necessary for which established procedures have not been defined. A great deal of this work is, of course, being done in those institutions operating under broad license; and it will be necessary to have cooperation between these highly specialized radiopharmacists, industry, and government, so that they can be brought together under the aegis of an independent organization which will help to write the guidelines of the research pharmacy, and to establish the procedures that are necessary where there are no established tests presently in existence.

Dr. Harper:

Our friends in the radiopharmaceutical industry have grown up in a world where they were faced with making products that had to sit on the shelf for days, weeks, or months. Many of the requirements that they are faced with are far beyond what might reasonably be considered necessary for a product that you would make and administer immediately.

Using the established principles that the radiopharmaceutical industry is faced with, possibly you might be leaning over backwards farther than is really necessary when you are using very short-lived isotopes.

Dr. Meyers:

You're not unique when you deal with radiopharmaceuticals and good manufacturing practice, as you don't have all the problems. I think we have to give industry a pat on the back as far as they have developed pharmaceuticals through trial and error over the years. At the present time (and in the last couple years), they have been trying to avoid many errors, and trying to get a good design in their experiments to find out what is good practice. The Society of Hospital Pharmacists has done something about this. They have problems in taking large volumes of solution, putting it into syringes, and getting it to the nursing stations in time to still be stable and useful to the patient.

You have almost identical problems here. You have radiation with it, but you're not unique in this problem. You take a solution and make 20 or 40 syringes. What testing do you do? Do you ignore this testing completely or have you set up a system that you think will work? You can't test all 40 of these syringes, or 20 (whatever number are involved). You have to use them, but sometimes they're not used within minutes or even hours. We all know this. In larger hospitals the syringes may sit for almost 24 hours, or over 24 hours, before they are used--reconstituted materials. The stability may be in question. These are the kinds of problems that you are concerned about--as well as sterility and being pyrogen free.

I think there is a need to study this problem in some group, whether it is pharmacy, the Society of Nuclear Medicine, or what have you. Get the information that is necessary so you can say, "this is workable, this is safe for the patient." This is all that good manufacturing process is, to get it to the patient so it is useful, safe and effective. I would like to see the design of an experiment, directed by some group--we'll all work on it and we'll say, "Well, this is the best we can do at this time." Then let's follow it. Otherwise, I think we are going off in different directions. It isn't something that is on "cloud 16," it's right with us and it's with us across the board, not just with radiopharmaceuticals. I think we can work with these other groups, taking into account the particular problems we have and the one you mentioned, the generators. They have been a real source of concern because the pharmaceutical firm can say, "This is sterile and pyrogen free when we ship it," but they don't know what your technician is going to do with it once it gets in the hospital. You do need good manufacturing practices there so that you can get this to the patient while it is still safe and effective.

Dr. Quinn:

I don't mean to oversimplify the matter, in regards to this comment, but everyone has mentioned the tremendous shortage of radiopharmacists, and Dr. Meyers mentioned that the problems we have in the hospital are no different than the problems that hospital pharmacies have in the extemporaneous preparations of various medicinals.

Our colleagues in industrial radiopharmacology and manufacturing have at their command, and in their experience, all of the drug manufacturing talents of the particular company for which they work, and despite the fact that our hospital pharmacists--and I speak of mine in particular--know nothing about radiochemistry, they do know a considerable amount of on-the-scene manufacture of safe-to-administer intravenous solutions, and we have used this talent in guiding us to better manufacturing techniques. We have also used this to stimulate an interest on the part of the pharmacists in radionuclide drug preparations so that the benefit here is a dual thing. I feel that although we may keep mentioning the fact that we don't have radiopharmacists, you will find a very interested party in your hospital pharmacist. Within this framework, the potential for development of trained radiopharmaceutical men in hospitals through pharmacy exposure is very great, and this is the way we are pursuing it.

Dr. Beierwaltes:

Dr. Quinn, could you elucidate further on who pays your pharmacist, where does he do the work, and where does he acquire his training with regard to radiation? This is precisely what I was trying to get at the other day, and I don't think this is clear in the minds of most of us, certainly not in mine. What is the ideal training for such an individual, or the environment in which he works? I would like to see the training of a radiopharmacist pretty well jelled, but any help at this stage would be helpful.

Dr. Quinn:

Let me just pass the question on to Bill Briner, who knows the situation very intimately, as my hospital pharmacist visited with him and Bill visited us.

Mr. Briner:

I will try to "field" that question for you in light of what has transpired here this morning. It becomes abundantly clear that most nuclear medicine groups, at this particular point in time, do not require the services of a high-powered, ivory-tower type of organic chemist--at least for the types of problems we are discussing at this time. These matters relate to the utilization of proper pharmaceutical formulation techniques--and most organic chemists have little competence in this area. As Dr. Quinn has indicated, there is a wealth of "in-house" talent available in most hospitals, and this talent includes, in many cases, highly competent hospital pharmacists who know from practical experience the types of problems one can encounter when pharmaceutical dosage forms are not properly formulated. On the other hand, they are fully cognizant of good manufacturing practices and the means which may be taken to avoid these formulation misadventures. What does it take to train these types of people so that they can be of direct assistance to you in nuclear medicine?

In my own laboratory--which as you know represents a full-time radiopharmaceutical service with both research and development and quality control missions--we have established only three basic qualifications which our incoming professional staff must possess. To be considered for assignment to my service, he must be a graduate pharmacist, he must have a strong background in the preparation of injectable products, and he must have had appropriate training in radiological health.

It is fortunate indeed for nuclear medicine that the first two of these requirements are adequately fulfilled by most hospital pharmacists, for it requires an expenditure of 6 to 10 years of formal study and some practical experience to gain these capabilities. The third requirement--adequate training in radiological health--can frequently be provided by the institution in which the hospital pharmacist practices. If this is not possible, the National Center for Radiological Health offers a variety of comprehensive short courses in this discipline that can be highly recommended.

My best advice to the nuclear medicine specialty is to seek the assistance of hospital pharmacists, use their broad knowledge of the various chemistries, and equally as important their unique competence in dosage form preparation. But you must provide them with sufficient training in radiological health or health physics to allow them to function in a manner which is compatible with their own safety, as well as that of their environment.

Dr. Harper:

We had an opportunity to observe this in action when our regular radiopharmacist, who has a master's degree in chemistry and who participates in the development of products, went on vacation for 2 weeks. We had to draft somebody from the regular hospital pharmacy. He came over for a couple of days, went through the cookbook, and was instructed in a few things. Actually, during the first week of our experience with him, he functioned adequately. During the second week, I must confess, he functioned considerably better than our regular radiopharmacist. The main problem in this area has been the fear that these people have of being exposed to what is relatively high-level radiation. Orientation rather than training is what these people need in order to function adequately with established preparations.

Dr. Ross:

This is a problem that will be with us for a long time and probably will increase. I know something about the difficulties of providing education in regard to nuclear medicine in medical schools, but what is the possibility of getting something about radiopharmaceuticals and health procedures introduced into the curriculum of pharmacy schools? Has there been any attempt to do this? Is there any mechanism which could be followed to get this instituted into the pharmacy curriculum?

Dr. Myers:

We have given a course on what would now be called nuclear medicine (a basic course) for the last 18 years, and we have been delighted in the last 6 years or so that from two to five of these so-called hospital pharmacists have been coming into this course, taking it along with their residency in various disciplines in the hospital, taking the regular course, taking all the examinations, and so on, to the point that at the present time I doubt if there are many, if any, of the hospital pharmacists at our institution that have not taken this course and taken all of the examinations.

It has been pointed out at this meeting repeatedly that practically no research on radiopharmaceuticals has been done by the radiopharmaceutical manufacturers, and that the great future of nuclear medicine, of course, lies in new twinkling molecules that will have high target-nontarget ratios. Cooperating with the Dean of our College of Pharmacy (who is just moving into a new building right next to our own), we have arranged that the pharmacists from the School of Pharmacy will continue to take this basic course, and then at a much higher level--at the 800 level, the master of science and doctoral level--we hope to come up with some new twinkling molecules that will have higher target to nontarget ratios. This is a solution as ideal as I know how to set it up.

Dr. Numerof:

Referring to Joe Ross' comments, I would just like to point out that industrial support has been given to the establishment of studies in radiochemistry in schools of pharmacy. There are three: one in Eastern Mississippi, there will be another in the Midwest, and another on the West Coast. These are schools of pharmacy that are offering courses in the broad subject of radiochemistry, with the idea of acquainting pharmacists with radioactivity and the techniques with respect to pharmaceutical problems.

Dr. Hilberg:

I would like to entertain only one more item on this particular subject. I think we are taking too long on the training of pharmacists right now. There are other things we have to discuss. Does anyone else care to have one last word on this training of pharmacists?

Mr. Cooper:

I would like to make the comment that most schools of pharmacy do have an elective radioisotope survey course; however, with the exception of a few that have been mentioned, these courses are devoted mainly to tracer techniques rather than being clinically oriented. Until the deans of the schools of pharmacy are made aware of the specific formulation problems that face nuclear medicine, these courses will continue to lack clinical orientation. That's part of the pharmacy curriculum problem.

Dr. Beierwaltes:

I am afraid I have held up some of the procedures and kept bringing this back, again and again, but probably I should announce that I've just made a decision which perhaps might precipitate further discussion, or at least simplify it. You recall I kept asking for a definition of a radiopharmacist, his job description, who is going to pay him, and so forth. I was not so interested in the theory of the training of the radiopharmacist as what are you actually going to do about this individual in your particular unit. I recounted that our radiation health physicist was leaving on September 1, to be head of nuclear medicine at a private practice hospital, and we have gone to our pharmacy and said, "We need help." But I think the problem is that none of us have really been able to jell this man's job description. The pharmacist said, "We need help too; why don't you have your radiation health physicist teach our pharmacists," so that's where we are currently.

The decision I have made is this: Our radiation health physacist is leaving and I am going to the pharmacy and say, "I want a pharmacist to take the place of the radiation health physicist in the clinical nuclear medicine unit. If you don't have a man who has had this training before, we will get him trained in radiation health physics. From now on we are not asking for a radiation health physicist in our unit, we are asking for a pharmacist. We will then make sure that he gets a radiation health physicist background." I think this is very pertinent to this discussion for two or three reasons. First of all, when the clinical units were young, we didn't have a problem for pharmacists, we had a problem for radiation health physicists. I think the discussion we have had here (today and yesterday) makes it clear that increasingly one of our major problems is now a problem for a pharmacist; that is, is this stuff that we reconstitute at the tableside really ready to go into a patient? The doctor and everybody seems to be equipped to decide whether it is a 1-microcurie dose or a 2-microcurie dose, or something of that sort. So this is the decision I have made here, that's been very helpful to me; and from now on this man will receive the pay that the radiation health physicist previously received, and the job description will be very clear to me.

Dr. Workman:

On Monday when we started this conference Dr. Moore asked us for the numbers of nuclear medical personnel needed. We all said that we needed technicians, pharmacists, instrument people, and physicians. But we really don't have any numbers. I would like to expand a little bit if we could on one of the things that came up in Group I yesterday, and which Dr. Quinn mentioned in the report (we also had some specific recommendations, as I recall). I realize that questionnaires are difficult to answer, and sometimes they don't really answer the questions. But since we already have a method, and a questionnaire group, who have all received these questionnaires from Ken Williams, wouldn't it be possible for us to expand the questionnaire? We could ask each one of these licensees how many technicians they now have, how many they need, how many instrument people they have, how many instrument people they need, and the same questionnaire would apply to pharmacists and physicians. Then we could get some idea about our manpower backlog, and find out if there is one. Is this feasible? Could it be done through the framework that is already set up? That is what I would like to know.

Mr. Williams:

In the second phase of the Stanford Research Institute's study which they are conducting for the National Center for Radiological Health, they are attempting to select a population that will represent the national population so that we don't burden everyone again with a second questionnaire. The second questionnaire will be directed toward obtaining more detailed information on nuclear medicine procedures. The questions will pertain to such things as patient characteristics, average administered activity, uptake and excretion, laboratory quality control, and so on. (I'm glad you brought up the question of training as I'm not sure that it was going to be in there, but it certainly should now.)

I am not sure how the Stanford Research Institute is going to select the census population to represent the total population. It will be small, but hopefully it will be representative of the national population.

Dr. McCormack:

I doubt whether the questionnaire that goes out to the present mailing list would adequately answer the question of the need for trained physicians or technicians, because there are a lot of smaller units that would like to get started but can't because they cannot find the proper personnel to do it. I doubt whether they would be reflected in this sort of questionnaire.

Dr. Workman:

There's one other part to this question too. In one of the reports this morning--I've forgotten which one--they said they thought that the supply of physicians was the first thing to work on, and then the technicians would follow.

I would like to differ very drastically with that. I think we have treated the technicians, as a group, very poorly, and I believe that this is getting to be a critical situation. I think that the technical people have to have some recognition and we have to do something. I don't have any solution to it, but I believe that before we can even give Dr. Moore and others an idea of how many people we need, we have to agree on what it is that these people have to know. The curriculum that has been partially agreed upon I realize has got to be established, and I certainly hope that we can do it. For 4 years we've been talking about it, but nothing has really been done.

Dr. McCormack:

I have a question for Group III. They reported a resolution for limiting the number of procedures by more regulatory statements or functions, and I would like to have that expanded a little bit. I would like to know the context of this regulatory function that is going to limit the number of procedures that we do.

Dr. Brown:

Where Group III mentioned that too many unnecessary and perhaps useless procedures have characterized some of the recent practices in this field, this is primarily a physician education problem, but also in part it is a licensing and/or regulatory problem. Let's assume there is a scanning procedure that has been adopted throughout the country which is actually worthless (this is my opinion of pancreas scans). I am not saying or advocating, for instance, that the FDA should just say, "Well, this is a nonefficacious procedure, so let's take selenomethionine off the market," but it is conceivable that there might be a procedure where this actually would be true--that the procedure is worthless. In that case I think it would be quite appropriate for the FDA or some other agency to act appropriately. That's why we felt it partly is a regulatory problem.

Dr. Mitchell:

The basic intent of that recommendation was that a reduction in the number of procedures in the nuclear medicine laboratory should be made by the physician who would act as a professional consultant rather than just offering a service. The decision to do or not to do a study should reside with him, and thus there would be a reduction in unnecessary studies that might otherwise be done in a laboratory if it acted purely in a service capacity.

Dr. Hilberg:

It's a broad use of the term "regulation," it appears.

Dr. Mitchell:

This is just a recommendation.

Dr. Davidson:

I was a member of Group III and I think that there were a number of members of this group who felt, as has been indicated here, that with the physician in the department of nuclear medicine making the determination of whether studies are done or not done, that considerable reduction in the number of studies could be accomplished, with no loss of important information for patient care.

There were several people in this group who indicated that 50 percent of thyroid scans or uptakes could well be eliminated if a professional man reviewed the indications for the study and operated his service as a consultative rather than a routine service with any Tom, Dick, or Harry ordering things whether he knows about them or not.

Dr. Harper:

This bothers me a little bit. What radiologist is going to refuse to take an X ray of a patient if the doctor orders it for the patient? How many of you here would turn down a thyroid scan if one of your colleagues sent him to you and asked for it. I don't quite see how this would function.

Another question I would like to raise (one that's been mentioned in a couple of the reports) is one regarding volunteers. I think it was even mentioned in our own group. The principle seems to be that an ordinary nuclear medicine procedure, such as you would do on a patient, is unacceptable on a volunteer because the radiation dose would be above the occupational limits. I was wondering if anybody would care to clarify this. I mean, if you want to study the excretion of a material after a liver scan or some other parameter, this obviously would entail more of a radiation dose than the occupational dose. We seem to be excluded from doing this by the recommendations from a couple of the groups.

Dr. Hilberg:

To speak to your first part, I can mention what our group had to say. We felt much the same as one of the other groups about the consultative service. The reason for this (as was pointed out by several in our group) was that many places have routines that an intern orders on every patient that comes in the room, and it should be checked whether this routine of thyroid scanning, or what have you, is really necessary for this patient. That's at least one of the philosophies that was presented in our group.

Dr. Kriss:

Just one other simple answer. I, for one, would refuse to scan anybody who was under my responsibility if I didn't want to do it, and I can get away with it quite well. It's a matter of education. A great many of the physicians (who are not very familiar with the procedure) do not even know the difference between an uptake and scan and an uptake alone. What they are interested in is the uptake. What they order is an uptake and scan because that's the kind of lingo which is, you know, built by association, if you will--and they don't realize that the dose is 10 times as much. It only takes a phone call once to a physician to educate him, and he'll say, "Oh, I didn't know that. Sure, let's not do that." That sort of thing, when repeated over and over again, could make a significant reduction in procedures.

Dr. Rajali:

If we don't review every patient (if we don't see every patient that comes, for example, for a thyroid scan), we will give a lot of tracer doses to a lot of patients and we're not going to get anything out of it. If the patient goes, for example, for an IVP and then comes to us for a thyroid uptake or some other examination, that patient has received, as you know, a radiopharmaceutical or other pharmaceutical that can ruin the uptake study. Therefore, we have to see these patients and we have to make a judgment whether or not we're going to do the procedure.

Dr. Cloutier:

I want to bring to the group's attention an article by Claude Sill regarding volunteers. He goes through some mathematical gyrations, I will admit, but he has considered this problem. You start a study and then after the study has been started, the volunteer decides he doesn't want any part of it, and how are you going to cease the exposure? You can't do it because the isotopes are in the patient and there is no way of getting it out quickly. So by choosing isotopes very carefully, the length of the study and different things like this, he comes up with a formula, and this is published in the 1966 Bioassay and Analytical Chemistry Conference.

I don't recall enough of the details, but he has a scheme regarding a weekly exposure, a monthly exposure, and a quarterly exposure.

Dr. Hilberg:

If I can sort of speak to the second part of your comment. The problem of volunteers is that we have something that is known as the professional volunteer, and this is the fellow who may walk in to one department and have a thyroid scan done. Then a liver scan is done the next day some place else (as a volunteer), and the third day have another scan done someplace else--none of these places being aware he is accumulating all of this material until they suddenly find out. It is conceivable that a volunteer could acquire a pretty heavy dosage this way. Although we feel there should be no discouragement of this, the key to it is informed consent by the volunteer.

SYMPOSIUM SUMMARY

Merrill A. Bender, M.D.[1]

Dr. Hilberg said, "Dr. Bender is going to summarize everything he has heard." It would be more correct to say that Dr. Bender is going to insert his own prejudices into the record!

I would like to touch on some of the recommendations that have been made and emphasize the obvious, as these proceedings may well reach a wider audience than the small group of experts gathered here today. Secondly, I would like to comment on the activities of the Society of Nuclear Medicine in several of the areas that you have brought up for discussion and recommendation, because I realize that although many of you are active members of the Society, you are not aware of the exact status of the Society's role at this time.

PATIENT DOSE

Needless to say, it is a delight to note that there was general agreement that diagnostic nuclear medical procedures do not deliver an excessive radiation dose to the patient, and that these doses are quite comparable with those delivered by diagnostic X-ray procedures. It was also noted, and I think very properly, that many of our diagnostic procedures provide information earlier in the course of the development of a disease than can be achieved by diagnostic X-ray studies. But what was not mentioned is that at least some of our studies provide unique information--information that is exceedingly difficult to obtain by any other means short of radical surgery. Obvious examples are the localization of frontal lobe tumors with brain scans, determining the functional capacity of thyroid nodules, detecting early pulmonary emboli, and detecting and localizing early space-occupying disease in such organs as the pancreas. All of these studies are unique, and play a positive role in the practice of medicine.

I was also happy to note that there was no great need expressed to reduce the radiation dose that our patients receive. I am very fond of the following expression, "The patient should not be protected out of a diagnosis." I felt that this particular sentiment was the feeling of this group in the past few days.

I certainly agree that an active role on the part of the physician in the clinical applications performed in his department can certainly reduce the number of "questionably necessary" radioisotope studies that are performed. It seems to me that as we develop more full-time people (or emotionally committed full-time if nothing else) then we tend to develop higher competence in those who can play this active physicians's role, rather than just act in a service capacity where studies are performed on a routine request basis.

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[1] Chief, Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo, N.Y. 14203

I was also happy to note that short-lived materials received considerable attention, but that they were not necessarily found to be the universal answer to our radiopharmaceutical problems. There were comments that some short-lived materials might not be physiologically appropriate for the studies involved, and I was particularly interested in the concern over time-dose relationships. I am in sympathy with those who would develop more radioactive compounds with short biological half-lives and long shelf-lives, as these endeavors would help us to develop the field even more rapidly.

Speaking of radiopharmaceuticals, I would like to review at this time the activities of the Society in this area. At the moment we have a Committee on Radiopharmaceutical Safety and Efficacy. This committee is composed of two subcommittees; one of which is the Medical Internal Radiation Dose Committee, with which you are all familiar; the other is an Efficacy Subcommittee which was designed to canvass the membership for clinical efficacy material, should it be required by regulatory agencies.

Several additional suggestions have been made in the past few hours concerning the role the Society could play in other areas. These might conceivably come under this same Committee on Radiopharmaceutical Safety and Efficacy and include: (1) the development of a Code of Good Practice for a radiopharmacy, and (2) the coordination of research efforts on the time-dose problem.

PERSONNEL DOSE

I think there was general agreement that both professional and technical personnel are receiving an increasing but not excessive exposure; and this is probably due to the increasing number of high activity generators present in most of our laboratories. I wonder if this problem is related to the fact that down through the years we have developed two systems of radiation safety procedures in our laboratories. One is for the therapeutic use of radioisotopes, and the other for diagnostic procedures, which in the past have always been at low activity levels. Now we are suddenly faced with the situation where our diagnostic levels approach therapeutic levels, and we have not adjusted our procedures accordingly. Obviously this sort of problem can be solved by reeducation, and conferences such as this one to bring these points to our attention.

EDUCATION

I would now like to address myself to education of professional personnel in departments of nuclear medicine--and first of all the physicians. At this stage in our development the most important step we can take to insure the needed number of competent physicians in the field of nuclear medicine is to establish boards in this specialty. When we have achieved this goal, we can look forward to the following:

1. Many more young physicians will enter the field, a step some are unwilling to take at this time because they cannot look forward to board status and the financial rewards that go with it.

2. We will have established residency programs, and with the resultant formalization of training requirements we could apply to Federal agencies to provide support for the training programs. With approved residency programs we would develop departments of nuclear medicine in medical schools, and these would be included in the curriculum with instructions to undergraduates.

3. Lastly, if we have board certification, this objective evidence of competence can help the regulatory agencies out of a unique situation; namely, that of passing on the competence of physicians to practice nuclear medicine.

The Society of Nuclear Medicine is making every effort to establish boards approved by the American Medical Association, but this is a long and difficult process. The first step is to have the Society recognized for identification after our names in the AMA Register of Physicians. This has already been done. The next step is to establish a Section of Nuclear Medicine at the AMA annual meeting. This takes about 5 years to accomplish, and during the interim we must hold nuclear medicine sections in the Miscellaneous Section. We have done this at the last three meetings, which brings us half way or a little better to our goal. Next we must set up an outline of what we would propose as a proper training schedule for residents in nuclear medicine. At the last annual meeting of the Society in Seattle, a tentative training schedule for physicians was established.

As an interim measure before nuclear medical boards are established, the Society is currently considering the creation of its own body to certify the competence of physicians and scientists. This could be done by evaluating the candidate's past experience and by examining him in the usual fashion. We are also examining the possibility of working through an established specialty examining board in the hope that this might expedite the creation of our own independent board.

We must also talk about continuing education. At annual meetings of the Society of Nuclear Medicine we try to promote continuing education of physicians by presenting a wide variety of refresher courses, and I believe these are extremely useful. It has been suggested in the past that the Society, in concert with others, might sponsor postgraduate training courses on specific topics in several population centers around the country. This idea is also being explored.

The Society of Nuclear Medicine's Committee on Technological Affairs has been working for some years to try to improve technician competence by achieving the following goals:

1. Establish training requirements and a curriculum for technologists that would be approved by the Council on Medical Education of the AMA and could be used by institutions of higher learning.

2. Establish a registry of Nuclear Medicine Technologists with proven competence. Both of these endeavors have been made in cooperation with the American Society of Clinical Pathologists and radiological societies, and hopefully this combined effort will achieve success in the near future.

We also have a program of continuing education for technologists in the form of special programs at the annual meeting of the Society. Quite recently we have tried to expand this by establishing councils for technologists in our local chapters. We hope that they in turn can establish training programs at the local level. This could be extremely beneficial since many technologists cannot obtain sufficient travel funds to attend the annual meeting. Here again, I feel, outside financial aid would be greatly appreciated and worthwhile.

In conclusion, Dr. Hilberg and his associates are to be congratulated on the success of this symposium. I am sure this was primarily due to their judicious choice of participants that brought together experts from the physical sciences, clinical practice, and government.

CLOSING REMARKS

Albert W. Hilberg, M.D.

I think that I can say, beginning with the rousing keynote by Dr. Saenger and the very informative remarks of Dr. Bender, we have stimulated the kind of dialogue that I hope will continue in this field. It has certainly been most helpful to us in the National Center for Radiological Health.

We have also probably accomplished part of the goal of the title of this symposium. We have, for at least 2-1/2 days (hopefully 3) reduced the exposure to patients from nuclear medicine practice by having all of you here.

On a more serious note, and to answer a question, the National Center has underway a revision of the Radiological Health Handbook. Also, I think of general interest, Dr. Bender has offered the use of the Journal of Nuclear Medicine as a vehicle for possible publication of a summary of this meeting.

I want to personally thank all of you for coming and spending this time with us, and I hope it has been as valuable to you as it has been to us.

Raymond T. Moore, M.D.

On behalf of our organization, the National Center for Radiological Health, this symposium has been most helpful, informative, and enjoyable. I do think we have something that will be appropriate for the Society of Nuclear Medicine's journal, and I think there have been opinions expressed here that are appropriate for all of us to study.

Thank you very much for your participation.

APPENDIX

University of Miami
Miami, Florida 33152

August 3, 1967

Dear

Thank you for responding to my recent questionnaire regarding the preparation of radiopharmaceuticals in your laboratory. Listed below are the results of this survey:

Number of institutions surveyed	60
Number of replies from institutions (as of 7/26/67)	46
Number of replying institutions that prepare radiopharmaceuticals	27

Tc-99m sulfur colloid preparation:

Number of replying institutions that prepare Tc-99m sulfur colloid	22
Number of replying institutions that have prepared Tc-99m sulfur colloid by two different methods	8

Tc-99m sulfur colloid prepared using	Number of institutions using this method	Number of institutions having reactions to material	Total number of "reactions" reported	Total number of procedures performed using material
H_2S-gelatin	12	2	3 minimal*	2,689 plus
Thiosulfate-gelatin	1	0	0	100
Thiosulfate-gelatin-perrhenate	3	0	0	410
Thiosulfate-dextran	6	4	7	942
Thiosulfate-dextran perrhenate	4	2	4	354
Thiosulfate-carboxymethyl cellulose	1	1	1 (pyrogen)	5
Antimony method	1	0	0	200
Commercial preparation	1	0	0	75

*Reactions may not have been directly associated with Tc-99m sulfur colloid

As one can see from the above table, there were 11 "reactions" reported for Technetium-99m sulfur colloid made using Dextran and, at the very most, three "reactions" using Gelatin (these could not be definitively associated with the Technetium-99m sulfur colloid). The percentage of reactions occurring with Technetium-99m sulfur colloid made with Gelatin is less than 0.1 per cent, while Technetium-99m sulfur colloid made with Dextran, the percentage is 0.9 per cent. It is also apparent from the study that the use of perrhenate cannot be associated with the reactions reported.

The reactions reported from the material made from Dextran were typically classified as "anaphylactic" or "anaphylactoid". The 3 reactions that occurred in our laboratory, we would classify as "a histamine type reaction". This consisted of the patient flushing, having a subjective feeling of being hot, and all of the patients complained of itching of both hands and feet. None of the patients developed hives. One patient had a severe drop in blood pressure requiring extensive and long-term medical support to restore him to his original status. The original condition of this patient was not good.

If those institutions which reported reactions to Technetium-99m sulfur colloid would please send me a brief clinical history of the reaction, and the subsequent condition of the patient, this would be greatly appreciated.

Our laboratory used Dextran 70 to prepare the Technetium-99m sulfur colloid. Depending upon how long after the colloid was prepared, each patient received between 5 to 15 mg. of Dextran, and in one instance, a patient received approximately 25 mg. However, this latter patient did not have a reaction from the material. I would greatly appreciate it if you would indicate to me the type of Dextran, i.e. molecular weight, that you are using to prepare your sulfur colloid, and the approximate mass that was administered to each patient.

It should be noted that the three reactions reported from our laboratory occurred on two different days, separated by several weeks. The day we had our first reaction, approximately three other patients had received the same material, and the day that we had the two reactions, one other patient had received the material.

Radiopharmaceutical	Number of institutions using this method	Number of institutions having reactions to material	Total number of reactions reported	Total number of procedures performed using material
Tc-99m Albumin	19	2	1(minor) +2(?)	776 plus
Tc-99m MAA	5	0	0	246 plus
In-113m Iron-DTPA	2	0	0	92
In-113m Gelatin colloid	1	0	0	100
In-113m Iron hydroxide (gelatin)	1	0	0	200
In-113m hydroxide (gelatin)	1	0	0	10

Of the institutions preparing Tc-99m albumin, 6 institutions have performed 10 or less procedures. None of the reactions from Tc-99m albumin were significant, and only one can be directly associated with the material. Two institutions reported that they had performed many procedures.

The information reported for the remaining radiopharmaceuticals was sketchy.

Again, thank you for your cooperation in this survey. If you have any additional comments or suggestions, they would be greatly appreciated.

Sincerely yours,

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U. S. GOVERNMENT PRINTING OFFICE : 1968 O - 293-599